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ORIGINAL ARTICLES

PROTEIN AND AMINO ACID REQUIREMENTS OF INFANTS

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IN ADDITION to the many metabolic functions of protein in adults, this primary foodstuff provides the child with the basic building materials required for growth. The protein needs for human growth are both qualitative and quantitative.[1] The available knowledge of these needs has been derived from N retention and growth of children maintained at varying levels of protein or specific amino acid intake. Because the protein requirements (and the same is true for fat and carbohydrate needs) are dependent on the relative amounts of all the other dietary essentials and the amino acid composition of the N moiety of the diet, all the data on this subject are as yet not at hand.

Some of the difficulties which encompass the measurement of the qualitative and quantitative needs of the child can be grasped from the variety of foods on which children have been found to grow. The analysis of natural and modified animal milks (table 1) used for infant feeding in various parts of the world demonstrate the differences as to the per cent of total calories in protein, lactose and fat which will support human growth.[2] It is obvious that in estimating the protein needs we have to consider not only differences in amino acid composition of the various milk proteins, but also the differences in caloric distribution. The nutritional advantages of these various milks for the human infant are a subject of much discussion among pediatricians. Unfortunately, the major portion of these discussions center about subjective, rather than objective observations. This is particularly true regarding comparisons of human and cow's milk. However, the recent work of Gordon and associates[3] clearly points to the conclusion that mixtures of cow's milk will produce larger gains in weight in premature infants than will human milk.

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TABLE 1

VARIOUS BIOLOGIC PRODUCTS EMPLOYED IN INFANT FEEDING

Milk Preparations	Total cal./cc.	Percentile Composition in Calories		
		Protein	Fat	Carbohydrate
Natural products:				
Horse	0.42	21	11	68
Ass	0.45	16	23	61
Goat	0.65	19	52	29
Camel	0.66	18	55	27
Llama	0.66	23	43	34
Cow	0.70	22	50	28
Man	0.70	8	50	42
Sheep	0.97	24	57	19
Water buffalo	1.51	16	75	9
Reindeer	2.23	20	75	5
Artificial mixtures:				
Condensed milk group	Average 1.0	10	25	65
Whey group		19	11	76
Cow's milk group		22	50	28
Protein milk group		30	54	16
Skimmed milk group		45	0	55

NUTRITIONAL LIMITATIONS OF HUMAN BREAST FEEDING

In this country, human or cow's milk constitutes the principal protein-containing food of early infancy. The protein content of human milk averages 1.25%; that of cow's milk, 3.5%. Since the proteins of both milks contain abundant and comparable amounts of all the amino acids essential for growth, the protein needs for growth are automatically met by providing sufficient milk of either variety. The concept of a higher biologic value of human over cow's milk, erroneously postulated on the basis of a cystine deficiency in the casein fraction, has been discarded since it was shown that methionine and not cystine is the sulfur amino acid required for growth of the human infant.[4] Indeed, this newer evidence supports the view that even on the most liberal intake estimates breast milk provides a very meager margin of safety during the early months of life and that it does not provide an adequate quantity of the sulfur amino acids in the latter part of the first year. On the same basis, cow's milk formulae seem to provide adequate amounts of sulfur amino acids. The supporting data for this view are presented graphically in chart 1.

Obviously, to have practical significance such a far-reaching deduction requires proof of greater statistical weight than can be derived from our few short term experiments. If amino acids are the only variable concerned, such evidence is afforded by the investigations of Su and Liang[5] and Hou[6] on the growth and development of Chinese infants under different nutritional environments. In order to reduce the effects of these conditions on the direction and speed of development to a uniform pattern, these data have been plotted on Wetzel Baby Grids.[7] This also provides a means of comparing objectively the growth of Chinese children who are for the most part breast-fed with what may be considered the average growth of American children who are for the most part artificially fed, or if breast-fed, receive supplemental food throughout infancy. The observed differences may

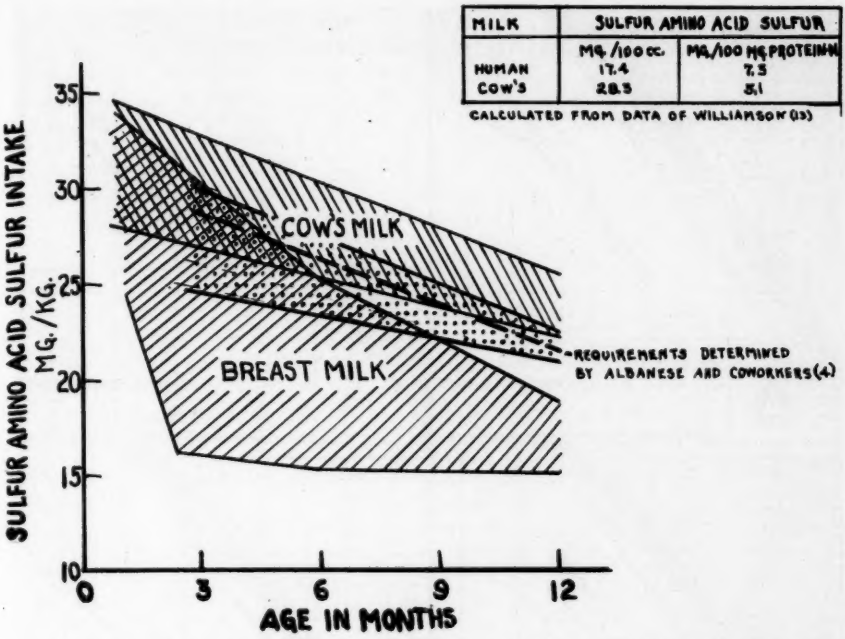

CHART 1. Diagrammatic comparison of sulfur amino acid sulfur provided by cow's milk and by human milk and measured needs of normal male infants. Values for human and cow's milk intake of infants were computed from best available data.

be due in part to racial characteristics. However, it is well known that racial differences with regard to height and weight change readily with an improved nutritional environment.

The results of the investigations of Su and Liang[5] are summarized in chart 2a.

These curves represent 949 records (561 males and 388 females) of infants followed in Well-Baby Clinics in the Hunan Maternity Hospital (1934-1937) and in the Pediatric Service of Hsiang Ya Medical College (1936-1937). Only those babies with sufficient breast feeding were included in this study. Twins, premature babies and those who had nutritional disturbances were excluded.

Examination of these data (chart 2a) would seem to fully warrant the following comments of these investigators: "The slow growth in the latter part of the first year may probably be explained on a nutritional basis—Parents usually do not take our advice that breast feeding meets the nutritional requirements of a baby for six months at most, while in the latter half of the first year, supplementary feedings should form the most important part."

The need for supplementary feeding in the latter part of infancy is even more dramatically demonstrated by the data of Hou[6] who reported on the height and weight measurements of infants (1202 males and 1005 females) in refugee camps in Shanghai during the period 1937-1938. These children who were also breast-fed for the most part show evidences of nutritional failure earlier than the infants studied by Su and Liang (chart 2b). This may be due in part to poor nourishment of the mothers which has been shown by

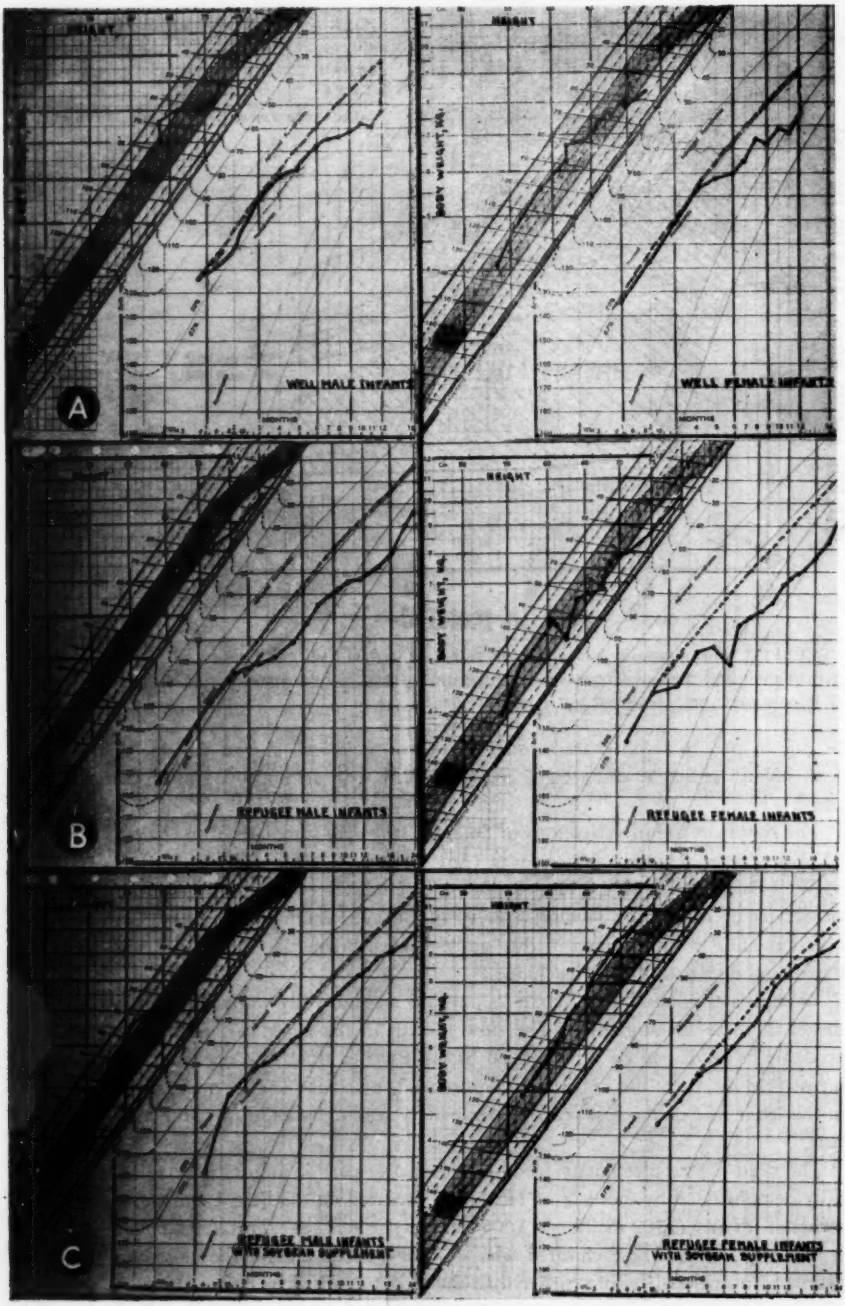
A
WELL MALE INFANTS
WELL FEMALE INFANTS
B
REFUGEE MALE INFANTS
REFUGEE FEMALE INFANTS
C
REFUGEE MALE INFANTS WITH SOYBEAN SUPPLEMENT
REFUGEE FEMALE INFANTS WITH SOYBEAN SUPPLEMENT

CHART 2.

TABLE 2

INFANT AMINO ACID REQUIREMENTS FOR NORMAL N-RETENTION AND BODY WEIGHT GAINS*

Mg./kg./day

Amino Acids	Cow's Milk Products			Beef Products			Wheat Gluten	Minimal Quantity‡
	Evaporated Milk	Casein (amigen ®)	Lactalbumin (edamin ®)	Beef Globin	Beef Muscle Protein	Beef Plasma Protein		
Arginine	127	160	140	141	206	245	126	126 b
Histidine	63	98	81	277	134	112	70	63 b
Lysine	200	264	304	304	320	342	80 (170)†	170 a
Tryptophane	47	70	87	59	93	49	30	30 a
Phenylalanine	177	199	213	250	169	182	246	169 c
Methionine	99	130	98	95	117	86	201	86 a
Threonine	151	157	206	257	234	245	87	87 b
Leucine	490	450	556	610	425	356	889	425 b
Isoleucine	167	251	227	36 (90)	102	126	195	90 a
Valine	171	263	161	298	227	266	182	161 b
Tyrosine	172	251	203	160	126	49	234	126 b
Cystine	27	18	109	18	38	19	46	18 b
Serine	160	227	172	182	201	—	—	160 b
Glutamic acid	680	800	470	200	650	588	860	200 b
Aspartic acid	166	222	340	283	380	370	350	166 b
Glycine	11	17	0	—	210	—	315	0 b
Alanine	75	196	98	280	140	—	175	75 b
Proline	250	286	140	185	210	—	350	140 b
Hydroxyproline	—	70	—	—	—	—	—	70 b

* These values were obtained from biologic value measurements of the author and his associates, and the best amino acid analytic data available for various proteins or protein products employed.

† Values in parenthesis indicate concentrations of amino acid after supplementation.

‡ The manner in which the minimal quantity values were obtained is indicated by the letters a, b or c which correspond to the designations employed in the text.

Smith[8] to have an important effect of birth weights and subsequent infant growth.

In a second phase of this investigation, Hou[9] studied the effects of a soy bean milk supplement on the growth and development of 322 children (152 males, 170 females) in the refugee camps throughout the first 2 years of life. The results of this work which are collected in chart 2c show clearly that the soybean supplement was very effective in preventing retrogradation of growth which befell the infants who received little if any dietary supplements during the latter part of infancy. Furthermore, these findings support in a statistically significant manner previous observations that soy bean protein can be used as an effective dietary supplement in infant feeding.[10]

CHART 2. Average growth of Chinese children under various nutritional environments. Broad dark band represents average height-weight ratio in normal growth. Migration of developmental curves to right indicates interrupted growth which is reflected more dramatically in auxodrome curves representing height-weight-age ratios. Expected auxodrome curves are represented by broken lines. Curves in Chart 2a show that under normal conditions, growth failure in breast-fed Chinese children occurs at about 5 months. This is indicated by deflections to right in both height-weight channels and auxodrome curves. In refugee infants (chart 2b) growth failure starts at 3 to 4 mo. of age and soybean supplement (2c) was reduced below level of that observed in well infants. According to is more severe than that experienced by well infants. Growth failure of refugee children receiving Wetzel, total nutritional deficit in each instance can be estimated from area bounded by expected and observed auxodrome lines.

Amino Acid Needs of Infants

It would be foolhardy indeed to ascribe the nutritional limitations of breast feeding completely to a lack of methionine without a consideration of other amino acid deficiencies which may arise from this practice. In order to do this we must examine the existing knowledge on the amino acid requirements of infants.

The available data on the amino acid requirements of infants (3 to 12 months of age) which are summarized in table 2 have been secured by the author and his collaborators[11] by three procedures: (a) determinations from the amount of amino acid needed to restore N retention and body weight gain to physiologic levels of subjects previously maintained for short periods on diets poor in the test amino acid, (b) estimation from minimal amino acid content of proteins and protein products found to have high biologic value in terms of N retention and body weight in infants and (c) calculations from "saturation point" of a test amino acid which is added step-wise to the diet of subjects maintained in normal N-metabolism by natural foods fed *ad libitum*.[12]

The values given in the last column of this table represent minimal quantities of each amino acid which should be present in the diet. Obviously, the amounts of the dispensable amino acids can be theoretically reduced to zero. However, this would impose metabolic stresses on the child which cannot be readily evaluated in terms of N balance measurements. Finally, the listed minimal quantities should be considered as useful approximations pending more exact determinations.

TABLE 3

Comparison of Amino Acid Needs of Infants and Amounts Provided by Normal Breast Feeding

Amino Acid	Estimated Daily Minimal Needs 3–12 mo.	Daily Amino Acid Intake Calculated for Normal Breast Feedings		
		3 mo.	6 mo.	9 mo.
	mg./kg.	mg./kg.	mg./kg.	mg./kg.
Arginine	126	108	80	74
Histidine	63	40	30	27
Lysine	170	150	113	103
Tryptophane	30	49	37	34
Phenylalanine	169	123	92	85
Methionine	86	46	35	32
Threonine	87	102	76	69
Leucine	425	365	274	250
Isoleucine	90	120	90	83
Valine	161	105	79	73
Tyrosine	126	275	206	189
Cystine	18	66	49	45
Serine	160	111	83	76
Glutamic acid	200	369	276	254
Aspartic acid	166	186	139	127
Glycine	0	0	0	0
Alanine	75	56	42	39
Proline	140	128	96	88
Hydroxyproline	70	—	—	—

On the basis of the available information, infants from 4 months to 1 year of age should receive protein 4.0-3.0 gm./kg. body weight.[1] Calculations from data on hand[13] show that the average breast-fed infant received approximately the following amounts of human milk protein (gm./kg.): 1 month, 4.0; 3 months, 2.4; 6 months, 1.8; 9 months, 1.6. It is at once apparent therefrom that the total protein intake of the completely breast-fed infant is far below the desired level after the third month of life. A comparison of the amounts of amino acids provided by human milk protein intake at various age levels and the estimated minimal needs established by the author's investigations is shown in table 3.

The values listed in the first column are those obtained by the procedure described above and those provided by human milk are calculated from the protein intakes and the analyses of human milk reported by Williamson.[14] It will be seen from these data that after the third month of life unsupplemented breast feeding which is still practiced in many parts of the world leads to not only a deficiency in methionine, but also to inadequate supplies of lysine, phenylalanine, leucine and valine. By the sixth month, the threonine supply becomes inadequate. The deficiency of these amino acids becomes more severe by the ninth month and is clearly reflected in the growth curves of the Chinese children shown in chart 2a, b and c. It is interesting to note that the tryptophane intake from human milk remains well above the determined requirement throughout this period.

Choice of Infant Food Supplements

Examination of the amino acid composition of various animal protein products shown in table 2 indicates that the nutritional shortcomings of breast feeding can be best corrected by supplements of milk or meat products. The relatively low isoleucine content of beef products is not of serious consequence since the breast-fed child receives an adequate supply of this amino acid throughout infanthood.

The cereal proteins, wheat and corn gluten, because of their lysine deficiency, would not appear to be satisfactory supplemental foods. The tryptophane deficiency of corn proteins is not critical since the tryptophane needs of the infants are covered by the mother's milk. However, the poor absorbability of corn gluten, possibly due to an amino acid imbalance, does not recommend the use of corn products.[15] On the basis of these considerations, the use of so-called Dutch Infants' Food composed of a mixture of butter, milk, sugar and flour, does not seem a rational procedure.[2]

The efficacy of soy bean flour as an infant food supplement has been amply demonstrated by Stearns and others in this country[10] and, as mentioned previously, by Hou in China.[9]

Amino acid hydrolysates have also been successfully employed by Magnusson[16] to reinforce human milk feedings. Although there is no question that protein hydrolysates should prove useful in this respect, it is difficult to see any nutritional virtues in these products which are not provided by the more tasteful and economical whole protein supplements.

Obviously, a simple increase in caloric intake achieved by the use of various carbohydrates and fat supplements does not correct the fundamental fault of total breast feeding practices beyond the age of 6 months.

Summary

Evidence has been presented which supports the view that the nutritional inadequacy of unsupplemented breast feeding of infants beyond the third month of life arises pri-

marily from quantitative rather than qualitative limitations of certain amino acids. On the basis of amino acid composition data and the biologic value of a number of proteins tested in infants, it appears that to overcome the defects of this feeding practice which still prevails in larger areas of the world the necessary diet supplements should be derived principally from animal protein sources, milk and meat, rather than cereal proteins. In the lack of animal foods, soybean milk may be employed to advantage.

References

1. Levine, S. Z., Protein nutrition in pediatrics, in Protein nutrition in health and disease, J.A.M.A. **128**:283, 1945.
2. Powers, G. F., Some observations on feeding of premature infants based on 20 years' experience at New Haven Hospital, PEDIATRICS **1**:145, 1948.
3. Gordon, H. H., Levine, S. Z., and McNamara, H., Feeding of premature infants: Comparison of human and cow's milk, Am. J. Dis. Child. **73**:442, 1947.
4. Albanese, A. A., and others, Sulfur amino acid requirements of infant, J. Nutrition **37**:511, 1949; also unpublished data.
5. Su, T. F., and Liang, C. J., Growth and development of Chinese children of Hunan province, Chinese M. J. **58**:104, 1940.
6. Hou, H. C., Height and weight measurements of young refugee children, Chinese Medical Association, Special report series Nos. 12 and 27, Shanghai, 1939.
7. Wetzel, N. C., Baby grid, J. Pediat. **29**:439, 1946.
8. Smith, C. A., Effect of maternal nutrition upon pregnancy and newborn, J. Am. Dietet. A. **25**:665, 1949.
9. Hou, H. C., Height weight measurements of refugee children given soybean milk, Chinese Medical Association, Special report series Nos. 12 and 37, Shanghai, 1939.
10. Payne, D. S., and Stuart, L. S., Soybean protein in human nutrition, Adv. Prot. Chem. **1**:187, 1944.
11. Albanese, A. A., Protein and amino acid requirements of mammals, in Protein and Amino Acid Requirements of Mammals, edited by A. A. Albanese, New York, Academic Press, Inc., 1950, pp. 115-151.
12. Albanese, A. A., Higgons, R. A., Vestal, B., and Stephanson, L., Phenylalanine requirements of children, Fed. Proc. **9**:144, 1950.
13. Holt, L. E., Jr., and McIntosh, R., Holt's Diseases of Infancy and Childhood, New York, 1940, pp. 14 and 177.
14. Williamson, M. B., Amino acid composition of human milk proteins, J. Biol. Chem. **156**:47, 1944.
15. Albanese, A. A., and others, Biological value of corn and wheat proteins in male infant with note on utilization of D-tryptophan, J. Nutrition **38**:215, 1949.
16. Magnusson, J. H., Amino acid mixtures as additional food for premature infants, Nature **154**:91, 1944.

Spanish Abstract

Requerimientos de Proteinas y Aminoácidos en la Infancia

Se presenta evidencia que confirma el concepto de que la deficiencia nutricional que ocurre en niños con alimentación materna no suplementada después del tercer mes, es causada principalmente por limitaciones cuantitativas mas que cualitativas de ciertos aminoácidos. Basandose en datos de composición de los aminoácidos y en el valor biológico de un número de proteinas probadas en niños, es aparente que para contrarrestar los defectos de esta alimentación, que aún prevalece en grandes areas del mundo, el suplemento necesario de la dieta debe obtenerse principalmente de proteina animal, leche y carne, preferiblemente a las proteinas de los cereales. En ausencia de alimentos animales, la leche de frijol de soya puede emplearse con ventajas.

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INTRACRANIAL COMPLICATIONS OF CONGENITAL DERMAL SINUSES

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CERTAINLY one of the most vulnerable incidents in embryology is the separation of the neuro-ectoderm from the epithelial ectoderm which occurs between the third and fifth weeks of intrauterine life. Failure of invagination of the primitive medullary plate to proceed in an orderly and complete fashion results in a wide variety of defects involving the skin and central neural axis as well as the surrounding structures of mesodermal origin.

Since this process is initiated along the mid-dorsal aspect of the embryo, it is natural for persistent cutaneous defects to be located along the midline posteriorly. Also, since the cleavage of neuro-ectoderm from epithelial ectoderm may be incomplete at any phase, it is logical to expect that a persistent cutaneous defect may extend anywhere from the deeper layers of the skin to the substance of the central nervous system or into the central canal of the brain or spinal cord.

The term generally applied to such a cutaneous defect when it persists as a space or tube lined with stratified squamous epithelium is congenital dermal sinus. At any point along a congenital dermal sinus, and particularly at its inner terminus, there may be expansion of the sinus into a cyst. Such a cyst is termed an epidermoid if it contains only epithelial debris and is lined by stratified squamous epithelium; it is called a dermoid if it contains, in addition, sebaceous materal and hair and the lining includes elements of the deeper layers of the skin. These cystic expansions may be little larger than the stalk itself or they may be relatively large expanding masses · there may be more than one cyst along the course of a single dermal sinus.

A cystic expansion of a congenital sinus which is located within the cranium or spinal canal may act as any other mass lesion to interrupt neurologic function by local compression or it may obstruct the normal circulation of spinal fluid. In addition, because of its persistent communication with the skin surface, it serves as a constant potential port of entry for infection into the central nervous system and its coverings.

Since the first report in 1926 by Moise[1] of staphylococcus meningitis secondary to a congenital sacral sinus, numerous reports have appeared of infection secondary to congenital sinuses along the spinal axis, particularly in the lumbo-sacral region. In 1949, Mount[2] collected 17 such cases with a history of infection and cited three other dermal sinuses of the spinal axis without infection. There are many others that have never been reported. Mount also described two instances of congenital dermal sinuses as a cause of intracranial infection and attested to the rarity of this situation by stating that no previous cases had ever been reported.

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INTRACRANIAL COMPLICATIONS
OF CONGENITAL DERMAL SINUSES

No.	Name	Age	Location of Dimple	Palpable Mass	X-Ray Defect	History of Infection	Location of Intracranial Extension	Result
1.	R.W.	3yrs. 1mo.	None noted	No	No	None	Cerebellum	Well; 8yrs.
2.	J P	10mo	Occipit	Yes	No	Meningitis Staph aureus	Cerebellum	Dead; 1mo post-op Hydrocephalus
3	A B	2yrs	None noted	No	No	Meningitis Staph aureus	IV Ventricle	Dead; 9mo post-op Hydrocephalus
4	L L	4wks	Occipit	Yes	Yes	Meningitis Staph aureus	Cerebellum and Cisterna Magna	Well, 2 1/2 yrs Has ventriculo-ureterostomy
5	E J	2yrs 8mo	Occipit	Yes	Yes	Meningitis No growth	Post Fossa extra-dural	Well, 2 yrs
6	J C	1yr 6mo	Occipit	Yes	No	Meningismus No growth	Post Fossa intra-dural	Well, 1yr 7mos
7	C D R	6mo	Occipit	Yes	Yes	Abscess Staph aureus	Cerebellum	Alive, 18 mos decerebrate
8	L B	6mo	Occipit	Yes	Yes	None	IV Ventricle	Well; 1yr
9	V K	1yr.	Bridge of nose	Yes	Yes	Osteomyelitis No growth	Frontal Fossa extra-dural	Well, 9mos
10	W P	8yrs 6mo.	Occipit	Yes	Yes	Abscess Staph aureus	Cerebellum	Well, 4mos

CHART 1. Summary of 10 patients with intracranial extension of congenital dermal sinuses.

MATERIAL

It is the purpose of this report to describe the clinical features of 10 patients seen at The Children's Medical Center with intracranial extension of congenital dermal sinuses, 7 of whom have been treated over a period of 2 yr. (chart 1). The results of treatment of these patients have been so poor when the proper diagnosis was made only after infection had already occurred as compared with results of prophylactic surgery previous to infection that the characteristics of this benign but potentially lethal lesion warrant careful description.

These 10 patients varied in age from 4 wk. to 3 yr. at the time of hospitalization; in 6, the correct diagnosis became apparent in the first year of life.

In 9 patients the congenital dermal sinus led into the posterior cranial fossa and in one into the anterior fossa.

DIAGNOSIS

The symptoms and signs characteristic of these lesions may be divided into two groups; first, those referable to the scalp sinus itself and secondly, those referable to intracranial complications.

1. Scalp: In or close to the midline a small dimple or sinus opening is usually seen.

Often one or more hairs protrude from the sinus, and there may be an absence of normal hair in an area 1 or 2 mm. in width adjacent to the sinus opening. It may sometimes be impossible to see such a dimple until the area is shaved and examined carefully under good light. There may or may not be "port-wine" staining of the surrounding skin. In most instances there has in addition been thickening of the scalp in this region or an actually palpable, movable, subcutaneous mass. In four patients there was a history of mild inflammatory reaction or drainage of thin yellowish fluid from the opening. A skin lesion was noted in 8 of the 10 patients; in 7, this was in the occipital region just above the external occipital protuberance (Figs. 1 and 2) and in one, at the bridge of the nose.

2. Intracranial Complications: These include symptoms and signs referable to the presence of a mass and those referable to intracranial infection; in some, the clinical picture has been due to a combination of both. Five patients had symptoms and signs indicating a mass lesion in the posterior fossa. These included headache, vomiting, ataxia, nystagmus, unsteadiness of gait, papilledema, extraocular motor weakness and hydrocephalus. In two of these, the tract from the skin was not discovered until operation for suspected cerebellar tumor; in the other three, skin lesions and bone defects were found during pre-operative investigation. In two, the posterior fossa mass proved to be a large abscess associated with a dermoid cyst in the cerebellum, and in the other three there was a cyst without abscess formation.

Meningitis was a primary feature in five patients. In three of these, Staph. aureus

FIG. 1. Appearance of small subcutaneous mass and abnormal hair distribution in Case 4.

hemolyticus was cultured and the other two showed no growth. Staph. aureus was also cultured from the two cerebellar abscesses. In every one of these patients the organism seemed peculiarly insensitive to chemotherapy.

There is an obvious inference in the foregoing statements, particularly to pediatricians; namely, that in the presence of an unexplained meningitis, especially due to Staph. aureus hemolyticus, the entire skin surface along the midline should be examined carefully for dimples, palpable thickening or sinus openings. This search should include shaving the head. In at least two patients of this series who were studied because of meningitis, the

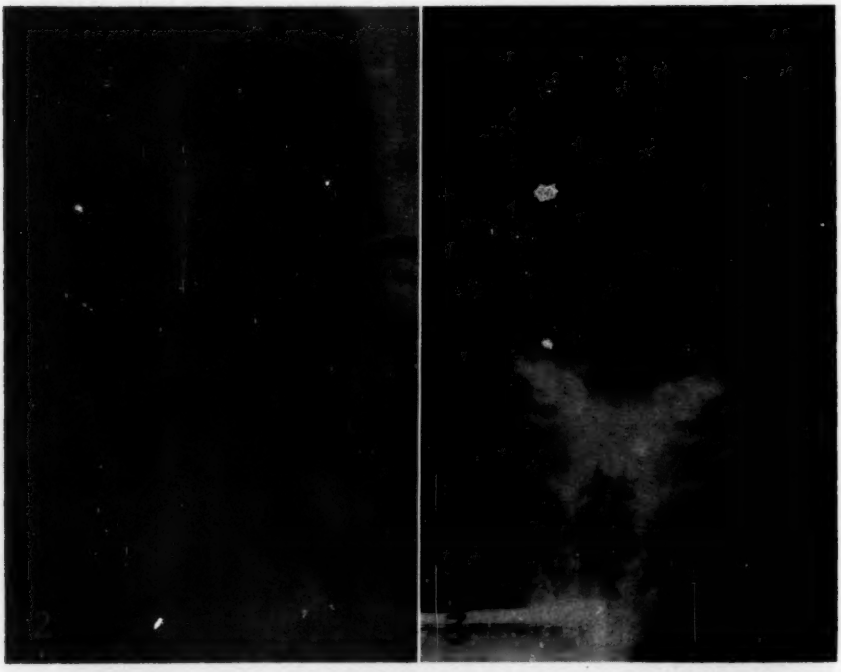

FIG. 2. Appearance of dimple, thickened scalp and small area of "port-wine" staining in Case 7.
FIG. 3. Midline, round, regular bony defect in occipital region (Case 7). Usually, defect in bone was much smaller than this and more angulated.

skin had been examined allegedly several times and reported negative until it was insisted that the head be shaved. A dimple was then seen and exploration disclosed a tract leading to a dermoid cyst within the cerebellum. In three patients it was possible to identify epithelial cells in the centrifuged sediment from spinal fluid obtained on lumbar puncture.

In addition to abscess and meningitis, a third type of infection was present in one case: acute osteomyelitis of the frontal and nasal bones. This produced edema, tenderness and redness locally, together with fever and leucocytosis, and was confirmed on roentgen examination and at operation.

ROENTGENOGRAPHY

In all these patients, obviously, there was a defect in the bone. This was demonstrable

at operation in every case, but it was not always apparent on roentgen examination. This is true because occasionally the path through the bone was little more than 1 mm. in diameter and it passed at such an angle that it was not readily visible in the conventional roentgenographic views. Usually, however, a definite, smoothly outlined, circular, midline defect of varying size was visible, particularly in an occipital projection (Fig. 3). It is probable that satisfactory roentgenograms will almost always demonstrate the path of the sinus through the skull if they are examined with this in mind. The inference that every child with a midline dimple or mass in the scalp should have a roentgenographic

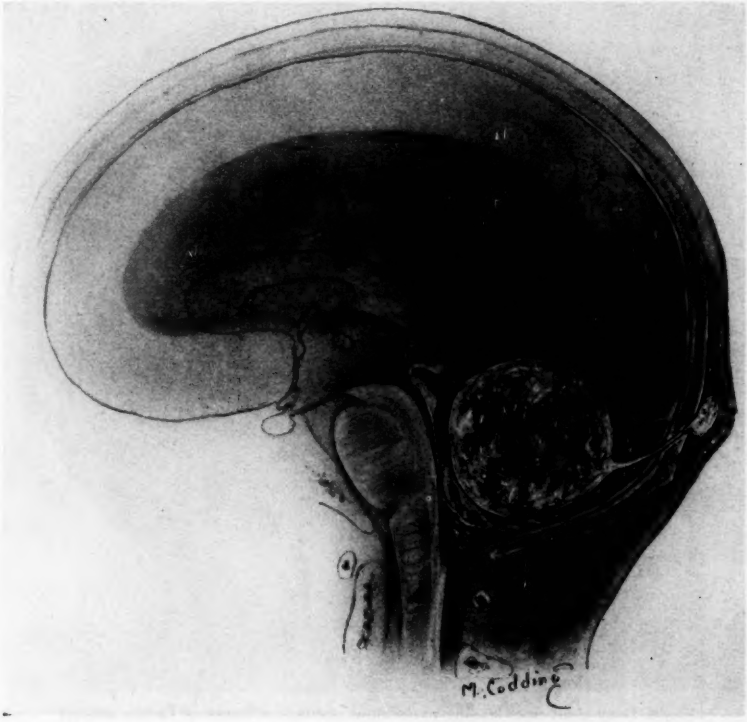

FIG. 4. Intracerebellar dermoid cyst causing compression of fourth ventricle and hydrocephalus (Cases 1, 2, 4, 7, 10).

examination of the skull is obvious. It is also fair to conclude that ventriculography which demonstrates symmetric hydrocephalus of the lateral and third ventricles in the presence of an occipital dermal sinus tract implies that this tract expands to a cystic obstructing lesion within the posterior fossa.

TREATMENT

The treatment of choice is surgical excision of the entire dermal sinus tract from the skin surface to its deepest projection, including all cystic expansions, before infection has occurred, or at least at a time when no infection is present. Therefore, when RGs have demonstrated a defect in the bone, or when there is any indication of increased intra-

cranial pressure, excision of a dermal sinus in the scalp should include preparation to carry out intracranial exploration as well. For the more common occipital lesions this will involve suboccipital craniectomy for exposure of the posterior fossa. In this series, occipital dermal sinus tracts were found to terminate within the meninges overlying the cerebellum in one patient, to expand terminally into a large extradural cyst in one patient, into a cyst within the substance of the cerebellum in five patients (Fig. 4) and into a cyst lying within the fourth ventricle in two patients (Fig. 5).

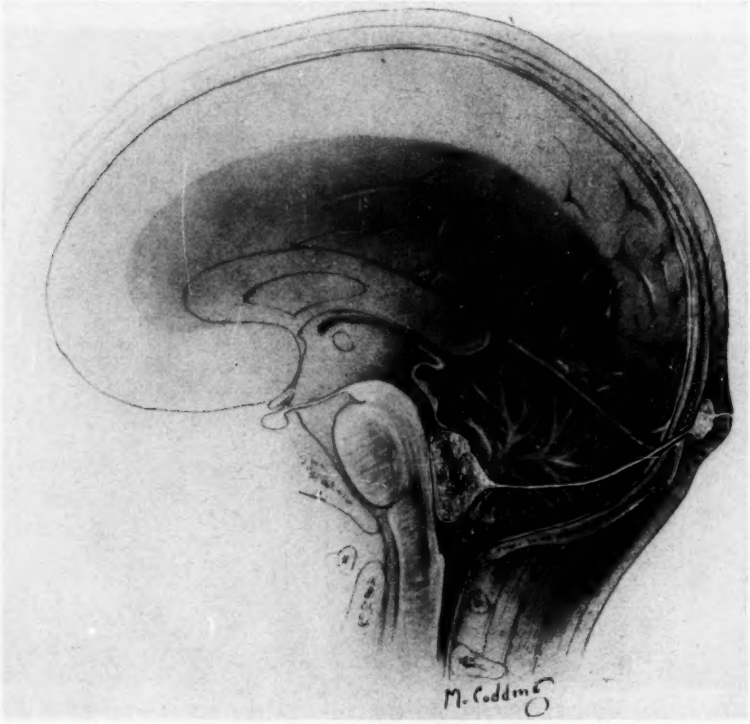

FIG. 5. Long sinus tract leading to dermoid cyst within lumen of fourth ventricle and causing hydrocephalus (Cases 3 and 8).

It should be pointed out that several of these patients had a dermoid cyst between the scalp and the bone, but from the inner surface of this small cyst the sinus continued on through the bone to a much larger cyst intracranially. That failure to recognize this can be a dangerous oversight is illustrated by one of the cases in this series:

Case 10: W.P. had a midline dermoid cyst of the scalp removed when he was 6 mo. of age. A thread-like stalk entering the bone was ligated. This patient returned 1 and 3 yr. later and had drainage of cerebellar abscesses by aspiration through a burr hole. He failed to return then for interim investigation as requested and was lost sight of until he was 8 yr. of age when he returned with symptoms and signs of increased intracranial pressure and a cerebellar mass lesion. At operation a huge dermoid cyst, 7 cm. in diameter, was removed completely from the posterior fossa (Fig. 6). His recovery and postoperative course to date (6 mo.) have been satisfactory.

The pathologic material obtained from these patients is unusual only in its site of origin. The sinus tracts through the scalp, skull and meninges consist of tubules lined by stratified squamous epithelium (Fig. 7). Infiltration of deeper layers with inflammatory cells varies with the amount of infection that has occurred. The cystic expansions within the cranium are also lined by stratified squamous epithelium and contain within their lumens large amounts of desquamated keratin, sebaceous debris and hair. If gross infection has occurred, the contents of the cyst may be liquid and contain many pus cells as well as bacteria.

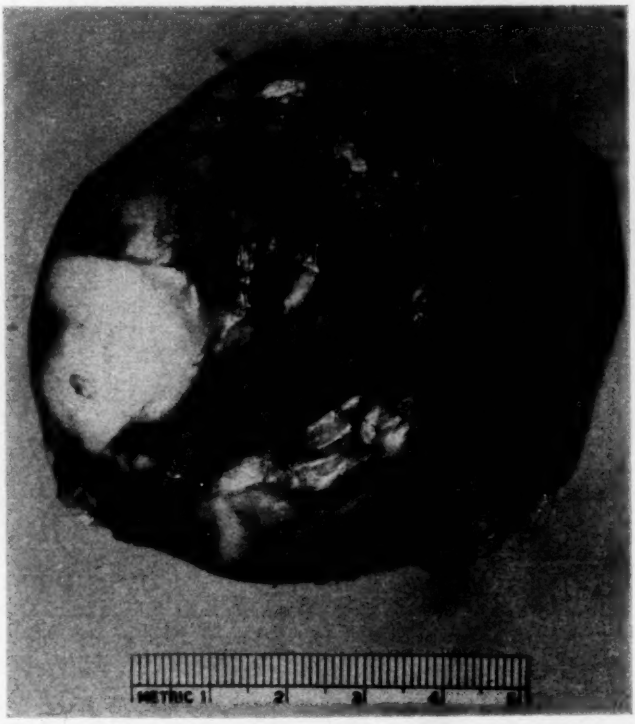

FIG. 6. Huge dermoid cyst completely removed from posterior fossa of 8 yr. old boy (Case 10). There was history of 2 "cerebellar abscesses" previously drained by aspiration through burr holes.

In the absence of infection, removal of a dermal sinus or cyst is relatively simple and the postoperative course uncomplicated. After infection, however, there may be marked inflammatory reaction of the cyst capsule with adhesions to all surrounding structures. If there has been leakage of the cyst into the subarachnoid space, an intense meningeal reaction usually results. In the two patients of this series who died with severe chronic meningitis and hydrocephalus, one after one month and one after nine months, there was virtually complete obliteration of all the subarachnoid pathways at the base of the brain. A third patient who had an abscess and severe chronic meningitis is still alive after 20 months, but is decerebrate.

Another patient with meningitis is worthy of presentation in a little more detail:

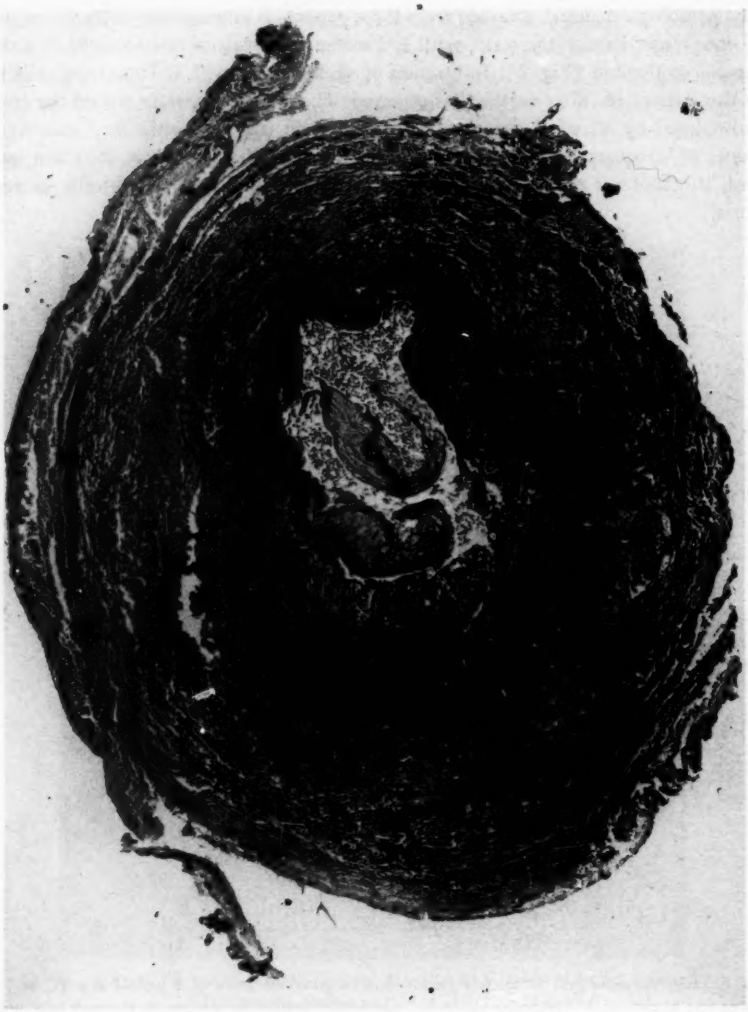

FIG. 7. Cross section of dermal sinus at level of penetration of dura of posterior fossa (Case 3). Note inflammatory reaction in wall.

Case 4: L.L. was admitted to The Children's Medical Center at the age of 4 wk. because of fever, vomiting and irritability. Investigation disclosed staphylococcus meningitis which responded slowly to antibiotic therapy. It was then noted the baby had a small soft tissue mass and dimple in the midline of the occipital region. RGs demonstrated a minute defect through the bone. A dermoid inclusion cyst in the scalp was excised together with a tract extending through the bone and down between the layers of the dura where it seemed to terminate in another small intradural dermoid cyst.

The patient was readmitted 3 mo. later because her head had grown in size too rapidly in the previous month and she had begun to vomit. At re-exploration still another small dermoid inclusion cyst was found in the right cerebellar hemisphere. However, the principal pathology was complete obliteration of the cisterna magna, the outlets of the fourth ventricle and the entire surface sub-

arachnoid pathways over the cerebellum and upper spinal cord by intense adhesive arachnoiditis, presumably a sequel to the staphylococcus meningitis. The cerebellar vermis was therefore divided and the fourth ventricle opened as widely as possible.

The patient did well postoperatively, but her head continued to enlarge. Right choroid plexectomy was therefore performed, and 6 wk. later, left choroid plexectomy as well. Repeated attempts to obtain spinal fluid by lumbar puncture during this period were unsuccessful. Following these procedures, increased intracranial pressure recurred again after a few weeks. It seemed apparent that this baby did not form spinal fluid rapidly, but that virtually none of it was being absorbed, presumably due to obstruction of the surface pathways. She was therefore readmitted and left ventriculo-ureterostomy performed.[3] Her pressure has since remained continually low, and she has not had to be tapped again in the 18 mo. since this operation.

It has been hard to sort out in this patient how much damage there may have been from the staphylococcus meningitis which was so difficult to control in the first few weeks of life, and how much from the long continued increased intracranial pressure, temporarily lessened by various operative procedures and taps and finally permanently relieved by ventriculo-ureterostomy. The child is now happy, alert and responsive; she eats well and is still improving. At 25 mo., she crawls and sits though she cannot yet walk alone. She has pale optic discs, but can see well enough to play with toys normally and recognize people across the room. She says quite a number of words. Her future progress will be followed with interest.

Contrast this long and complicated course with that of another patient:

Case 8: L.B. was admitted to The Children's Medical Center at the age of 6½ mo. At birth a small, soft cystic swelling was noted in the midline of the occipital region which, however, had not changed appreciably in size. Three weeks before admission the skin overlying this lesion became inflamed and reddened and was said to have drained some yellow material for a period of about 5 days. The patient had no fever or stiff neck. In the midline of the occipital region there was a subcutaneous, fluctuant, movable swelling about 4 to 5 mm. in diameter. There was a tiny dimple in the skin overlying this and from it several long hairs protruded. RGs revealed a 3 mm. defect in the midline of the occipital bone.

The subcutaneous mass and dimple were excised disclosing a subcutaneous dermoid cyst which was found to connect with a dermal tract leading through the defect in the bone. The tract extended caudally for a distance of about 1.3 cm. in the diploe, penetrated the inner table and then the dura overlying the posterior fossa between the cerebellar hemispheres at a point just below the torcula. As the sinus tract was followed downward, it was found to expand into a dermoid cyst approximately 2½ cm. in diameter, which lay between the hemispheres of the cerebellum displacing the vermis and extending down to the roof of the fourth ventricle. The cyst was evacuated and the cyst wall was teased out. There was no evidence of acute infection or contamination of the subarachnoid space. The stalk did not seem to extend beyond this mass. The fourth ventricle was approximately normal in size.

Postoperative course was uneventful. The operative wound healed primarily and the patient's development in a year since operation has been satisfactory with no evidence of infection or hydrocephalus.

A simple comparison of the clinical course of these last two patients, one infected and the other not, emphasizes the lesson to be learned from this report. Abbreviated protocols of the other seven patients are now presented:

Case 1: R.W. was admitted at the age of 3 yr. because of vomiting of 1 wk.'s duration. She was dehydrated, semistuporous, and showed papilledema and hyperactive reflexes. RGs revealed a small round defect with sclerosed edges in the middle of the occipital bone. At operation a dermal stalk was found leading from the deeper layers of the skin through the bony defect and dura and expanding into a dermoid cyst 4 to 5 cm. in diameter within the right cerebellar hemisphere and vermis. There was evidence of recent inflammation with adhesions to the cerebellum and tentorium. She did well for 10 days after operation, then developed high intracranial pressure again. Third ventriculostomy was performed and the posterior fossa was re-explored with freeing of adhesions about the cerebellum and cerebello-pontile angles. She then did well and has remained asymptomatic for 8 yr.

FIG. 8. Sinus tract leading from skin to large extradural dermoid cyst within posterior fossa (Case 5).

Case 2: J.P. was admitted at 10 mo. of age because of stiff neck, vomiting and fever of about 2 mo.' duration. He was poorly nourished, dehydrated and irritable. A small soft mass was noted in the midline of the occipital region which had been seen to ooze clear fluid according to the family. Spinal fluid was under increased pressure and showed 100 to 120 WBC but a negative culture. At operation a dermal tract led from the subcutaneous mass through the occipital bone at an angle and expanded into a large grossly infected dermoid cyst lying between the cerebellar hemispheres and filling the caudal half of the fourth ventricle. The cyst was dissected free with considerable difficulty and several adherent areas were left behind. Postoperatively he ran a gradual down-hill course and died 2 mo. later in spite of ventricular drainage and intensive chemotherapy. At autopsy there was marked hydrocephalus with tenacious thick exudate obliterating the basilar cisternae.

Case 3: A.B. was admitted at the age of 2 yr. because of headache, irritability, weight loss and vomiting. Examination showed hyperactive reflexes, staggering gait, rigidity of the neck and malnutrition. Skull RGs showed no defect but slight separation of the sutures. Ventriculograms revealed

internal hydrocephalus with no visualization of the fourth ventricle. At operation a dermal tract was found penetrating the bone at an acute angle and continuing in the midline through the posterior fossa to expand into a dermoid cyst 2 by 2.5 cm. which lay in the caudal half of the fourth ventricle. It was closely adherent to the walls but not the floor of the ventricle. There was epithelial debris floating freely in the spinal fluid within the cisterna magna and cerebellopontile angles. Postoperative course was stormy with swinging fever and positive spinal fluid cultures for Staph. aureus hemolyticus which resisted all types of drug therapy. He deteriorated steadily and after a period at home was readmitted to the hospital for terminal care. Autopsy revealed marked hydrocephalus and obliterative chronic basilar meningitis.

Case 5: E.J. was admitted at the age of 2$\frac{8}{12}$ yr. because of intermittent fever and irritability of 2 wk.' duration. She was irritable and febrile and had a slight divergent squint. Spinal fluid was under normal pressure but showed 200 WBC, which on detailed examination proved to be mostly degenerated epithelial cells. After the scalp was shaved a small subcutaneous nodule was discovered in the occipital region with a tiny dimple in the overlying skin. RGs showed a midline bony defect 2 by 3 cm. At operation a dermal stalk was found leading from the subcutaneous nodule through the bone to expand immediately into a dermoid cyst 3.5 cm. in diameter which lay protruding into the posterior fossa extradurally (Fig. 8). It was closely adherent to the much thinned out dura with evidence of recent inflammation. Culture of material from within the cyst revealed B. coli. During 2$\frac{1}{2}$ yr. since removal of the cyst, this patient has shown no evidence of infection or hydrocephalus and has developed normally.

Case 6: J.C. was admitted at the age of 18 mo. with a history of local infection about 2 small masses and a dimple in the skin of the occipital area. Three months previously the child was hospitalized elsewhere with fever and a stiff neck. No bony defect was seen on roentgen examination. Spinal fluid showed 20 WBC and a negative culture. At operation a dermal tract was found leading from the more medial of the 2 subcutaneous masses; it penetrated the bone at a very acute angle and entered the dura of the posterior fossa in the midline, apparently becoming attenuated in the arachnoid without expanding into a cyst intracranially. The pathologic diagnosis was dermoid cyst of the scalp and dermal sinus tract. The postoperative course to date has been uneventful.

Case 7. C.D.R. was admitted to the hospital at the age of 6 mo. because of fever and cough. Clinical and roentgenographic evidence of pneumonia subsided under chemotherapy. A dimple was noted in the suboccipital area from which protruded a single long hair; RGs of the skull revealed an underlying defect in the skull 1 cm. in diameter. Because of the severity of the pneumonic infection the child was sent home for further convalescence before posterior fossa exploration. However, the patient did not return as directed and was subsequently admitted 12 mo. later because of fever, lethargy and vomiting. Examination now showed papilledema, a bulging fontanelle and high fever. The baby's condition seemed precarious and she was placed on constant ventricular drainage. In spite of chemotherapy, extensor rigidity and opisthotonos appeared rapidly, so that the posterior fossa was explored. A dermal tract was found leading to a completely broken-down, grossly infected enormous dermoid cyst occupying practically the whole right cerebellar hemisphere. The mass was evacuated but the capsule was completely adherent to the surrounding tissues. The patient's condition was precarious at all times and the postoperative course stormy. Her extensor rigidity and opisthotonos persisted. Spinal fluid circulated as far as the posterior fossa and spinal canal but not beyond. In spite of ventricular drainage and chemotherapy she continued to deteriorate. It was apparent that she was probably blind and decerebrate, so she was discharged to a nursing home for terminal care.

Case 10: V.K. was admitted at the age of 1 yr. because of an increasing swelling in the middle of the forehead with tenderness and edema of the upper eyelids. At birth a tiny dimple had been noted in the skin of the bridge of the nose. Skull RGs showed an irregular defect in the frontal bone 14 by 18 mm., the margins of which showed evidence of active bone destruction. At operation a dermal tract was found leading from the skin dimple to a broken-down infected dermoid cyst between the scalp and the frontal bone. The edges of the bone were obviously infected and showed osteomyelitis microscopically. The cyst extended through the bone by a narrow neck and expanded to a much larger portion intracranially closely adherent to the dura and extending up for a distance of about 4 cm. under the frontal bone. As the capsule was dissected away from the adherent dura and longitudinal sinus, an extension was found through a defect in the cribriform plate expanding to another cyst in the nose. There were no complications after complete excision of the infected cyst and bone and the patient has remained asymptomatic.

Results

The results of these 10 patients are summarized in chart 1. It should be noted that in the patients properly diagnosed only after severe infection had occurred there were four unsatisfactory results: two deaths as a result of chronic meningitis and hydrocephalus; a third patient, still alive but decerebrate after 20 months; a fourth patient finally cured of meningitis but relieved of progressive hydrocephalus only by ventriculo-ureterostomy. The other six patients are alive and asymptomatic from 6 months to 8 years after surgery.

Summary and Conclusions

Ten patients are presented in whom intracranial extension of a congenital dermal sinus was disclosed by operation. The complications of this lesion include infection in the form of meningitis, abscess formation and osteomyelitis as well as hydrocephalus due to obstruction of the spinal fluid pathways.

In unexplained meningitis, the entire midline area of skin over the neural axis should be examined carefully for evidence of a dermal sinus opening. Whenever a dimple or subcutaneous mass is found in the midline of the scalp, RGs should be examined carefully for an underlying skull defect. When such a defect exists, intracranial exploration is indicated.

Surgical treatment previous to development of intracranial infection is relatively simple and should be rewarded by complete cure. Excision after infection has occurred is difficult and the results in this group have been poor.

References

1. Moise, T. S., Staphylococcus meningitis secondary to congenital sacral sinus, Surg., Gynec. & Obst. **42**:394, 1926.
2. Mount, L. A., Congenital dermal sinuses as cause of meningitis, intraspinal abscess and intracranial abscess, J.A.M.A. **139**:1263, 1949.
3. Matson, D. D., Ventriculo-ureterostomy, J. Neurosurg. **8**:398. 1951.

Spanish Abstract

Complicaciones Intracraneales de las Fistulas Congénitas Cutáneas

Cuando el clivaje neuroectodermico del epitelio ectodermico es incompleto, una fistula cutánea persistente puede extenderse en cualquier sitio desde las capas profundas de la piel hasta el canal central del cerebro o medula espinal. Estas fistulas han sido descritas frecuentemente en la region lumbo-sacra pero no intracranealmente. Los autores describen diez casos en los cuales la extensión intracraneal de una fistula cutánea congénita fué descubierta durante la operación.

Las complicaciones de ésta lesión incluyen infección en forma de meningitís, formación de abscesos y osteomielitís así como hidrocefalia debido a la obstrucción de la circulación del liquido cefaloraquideo. En meningitís inexplicables, el area completa de la linea media de la piel sobre el eje neural debe ser examinado cuidadosamente para descubrir la presencia de un orificio de fistula cutánea congénita. Dondequiera que un "dimple" o tumor subcutáneo es encontrado en la linea media del cuero cabelludo (scalp), radiografias deben ser examinadas cuidadosamente por la presencia de defectos del craneo. Cuando el defecto existe, la exploración intracraneal es indicada. El tratamiento quirurgico previo al desarrollo de infección intracraneal es relativamente simple y debe resultar en una curación completa. La intervención quirurgica (excisión) después que la infección ha ocurrido es dificil y los resultados en este grupo han sido pobres.

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EFFECT OF THE CAROTID-JUGULAR-ANASTOMOSIS OPERATION UPON INTELLIGENCE

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THIS paper presents the psychologic observations which were made with respect to the intellectual status of 33 children before and after the carotid-jugular-anastomosis operation (c-j-a). This operation, as previously reported by Beck and McKhann,[1] was designed to increase the cerebral circulation in the hope of improving the mental abilities of retarded children as well as procuring other beneficial effects in children and adults suffering from such physical disabilities as convulsive disorders and sensory-motor impairment.

The 33 cases reported in this study are all cases of children who had had standard psychometric tests before surgery and who were referred to the psychologists of the University Hospitals for postoperative testing. The time elapsing since surgery varied from one month in one instance to two years in another instance (see table 2), the median time interval being 11 months. It is possible that in some of these patients the anastomosis was not functioning properly at the time of the postoperative examination, and in one case the anastomosis had already undergone revision (see table 2, Group I, Case 4). Of these 33 children, 24 had been tested before the operation by the psychologists at the University Hospitals, and 9 had been tested by qualified psychologists in other institutions.

The preoperative intelligence tests which are reported are the Cattell Infant Intelligence Scale for those children with mental ages below 2 years, and the Revised Stanford-Binet for those children above this mental age level. Postoperatively, the parallel form of the preoperative Stanford-Binet was administered or the Cattell Scale was repeated.

NATURE OF THE GROUP

The patients were all below the limits of average intelligence to a greater or a lesser degree. According to McKhann, Belnap and Beck,[2] "There must have been normal development with subsequent injury before this operation would have rationale." These cases, therefore, were selected for operation on the basis that the children were the victims of an organic brain damage which resulted in their mental retardation.

For the psychologists, these children presented a variety of problems in the accurate measurement of intelligence. Because of these difficulties, the cases have been divided into two main groups:

The first major group consists of 22 children with various degrees of mental retardation but without evident physical symptoms that would complicate test procedures. This group has been subdivided according to the degree of retardation indicated by postoperative testing, as shown in table 1.

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TABLE 1

DISTRIBUTION OF CHILDREN AMONG CLASSIFICATIONS OF MENTAL RETARDATION

Dull normal (I.Q.'s between 80 and 90)	1 case
Borderline defective (I.Q.'s between 65 and 80)	1 case
Moderately defective (I.Q.'s between 50 and 65)	6 cases
Grossly defective (I.Q.'s between 35 and 50)	9 cases
Virtual amentia (I.Q.'s unmeasurable up to 35)	5 cases
Total	22 cases

TABLE 2

Case No.	Age at Time of Operation (to Closest Yr.)	Prior Test M.A.		I.Q.	Time Elapsing Between Operation and Follow-up	Postoperative Test M.A.	I.Q.	Comments as to Effect of Operation
					Group I			
					mo.			
1	7	4–9		70	10	6–11	88	Apparent rate increase
2	11	5–3	(1946)	68	6	8–6	72	Development continuing at same rate
3	13	6–8		50	5	7–2	53	Development continuing at same rate
4	4	2–3		52	17	3–0	50	Development continuing at same rate
5	6	3–10		63	10	4–4	61	Development continuing at same rate
6	8	5–10		59	3	6–0	59	Development continuing at same rate
7	3	2–0		63	5	2–3	63	Development continuing at same rate
8	1–8	0–11		55	5	1–1	50	Development continuing at same rate
9	8	3–2		38	5	3–3	38	Development continuing at same rate
10	5	2–5		47	6	2–7	45	Development continuing at same rate
11	4	2–0		50	13	2–4	46	Development continuing at same rate
12	14	4–10		36	5	5–0	35	Development continuing at same rate
13	14	4–3		35	13	4–7	34	Development continuing at same rate
14	9	4–4		46	16	4–7	43	Development continuing at same rate
15	7	2–6	(1948)	44	8	3–6	47	Development continuing at same rate
16	4	1–1		27	13	1–10	34	Development continuing at same rate
17	6	2–0	(1948)	44	12	3–0	44	Development continuing at same rate
18	0–6	0–2		30	12	0–2	10	No change in mental age
19	1–6	0–5		27	12	0–8	26	Development continuing at same rate
20	3	0–8		35	14	0–10	20	No change in mental age
21	15	5–0	(1945)	49	9	No relevant responses		No effect on intelligence or behavior
22	10	2–4	(1944)	52	10	No relevant responses		No effect on intelligence or behavior
					Group II			
23	10	3–0		30	16	3–0	25	No change in mental age
24	4	2–9		69	6	2–11	64	Development continuing at same rate
25	3	1–7		54	12	2–6	64	Apparent rate increase
26	11	6–0	(1948)	60	10	6–0	52	No change in mental age
27	1–2	0–2		15	15	0–2	12	No change in mental age
28	6	1–10		34	11	2–0	30	No change in mental age
29	4	2–10		75	19	3–0	55	No change in mental age
30	4	1–3		30	3	1–4	31	Convulsions have been relieved
31	4	1–0		30	1	1–0	31	Convulsions have been relieved
32	4	No responses			15	No responses		No change in mental age
33	7	No responses			15	No responses		No change in mental age

The second major group consists of those children who were mentally retarded and who also had major physical defects which complicated standard testing procedures; namely, five spastic children and six children with frequent grand mal or petit mal convulsions.

Discussion of Psychometric Results

The data of this study are presented in table 2. The following is a discussion of the particular problems and observations pertinent to the separate subdivisions.

Group I

Dull Normal Retardation (1 case): One child obtained an IQ of 88 following the operation, which is not significantly below the lower limit for average intelligence (90). Prior to surgery, he had obtained an IQ of 70 with another (extramural) examiner. This boy of 7 years had the complicating factors of strephosymbolia and poor visual-motor coordination. The rise in I.Q. may be due to the change in type of questions asked at the higher age levels in the Stanford-Binet, where greater emphasis is placed upon verbal reasoning ability in comparison with visual-motor tasks; or the rise in I.Q. may reflect the beneficial effect of the anastomosis.

Borderline Defective Retardation (1 case): The I.Q. of the child in this classification increased from 68 to 72, a change which does not exceed normal expectancy for Binet retests.

Moderately Defective Retardation (6 cases): Six children fell into this classification, with I.Q.'s ranging from 50 to 63. It has been previously reported[2] that the greatest benefits from the c-j-a operation are to be found in children with I.Q.'s from 40 to 60. In the six cases reported in this paper, the I.Q. changes are all within five points, which is within normal expectancy for repeat psychometric examinations, and there is no consistency in the direction of the I.Q. change.

Grossly Defective Retardation (9 cases): There were nine children who obtained I.Q.'s ranging from 34 to 47. In no instance was the change in mental age greater than that which would be expected from the rate of mental growth originally indicated by the preoperative intelligence quotient. The greatest change in I.Q. was seven points; the other eight patients showed changes of less than five points.

Amentia (5 cases): With the five children in this category, the test results either were unmeasurable, because of lack of sensible response, or yielded an I.Q. below 30. One of these cases has been previously reported (Case N.N.[1]); the most recent findings for this child are therefore given in detail:

Case 19. This little girl was operated upon at the age of 18 mo. It was reported[1] that she progressed from a mental age of 5 mo. to one of 7 mo. in a 2 mo. period following the operation. A year later she was tested again and was found to have a mental age on the Cattell Scale between 32 to 36 wk. (approximately 8 mo.). She did not continue to make the progress that was recorded initially and when she was 3 yr. of age, the operation was revised. The most recent test was done 5 mo. later, when she obtained a Cattell mental age of 9 mo., which yields an I.Q. of 21. Her rate of mental growth seems to be about 1 mo./yr., which is approximately the same as before the revision of the anastomosis.

Group II

Spasticity (5 cases): Of the three moderately defective spastic children (I.Q.'s between 50 and 64), two obtained lower I.Q.'s by eight and five points on the postoperative examination when compared with the preoperative test, and one showed an increase of 10

points. The case of increase in I.Q. seemed to be the result of the test construction; standard test questions at this child's preoperative chronologic age level (3 years) are heavily weighted with motor abilities, so that his first test score was particularly influenced by his motor handicap, whereas his second test (a year later) included a greater proportion of purely verbal items.

The remaining two children in the spastic group obtained postoperative I.Q.'s below 30 and showed no change in mental age.

Convulsive Disorders (6 cases): Of the six children with a major complaint of frequent convulsions, one child had a postoperative I.Q. above 50. This case was previously reported by Beck, McKhann and Belnap a few weeks after the operation (Case L.C.[1]); subsequent test results are therefore given in detail:

Case 29. This boy was operated upon at the age of 4 yr. One month prior to the operation, he achieved a mental age of 2 yr., 10 mo., and an I.Q. of 75, which is classifiable as borderline defective. He was not tested again until 19 mo. after surgery. He then obtained a mental age of 3 yr., 0 mo., and an I.Q. of 55. His parents reported to the examiner that for 6 mo. following surgery, he was virtually mute and only gradually regained his former abilities.

Three children in this group obtained I.Q.'s below 30 and showed very slight change in mental age level following the operation. However, two of these children presented an improved appearance a few weeks postoperatively in that they were more cheerful and more interested in their environment. There was as yet no measurable increase in the ability to perform set tasks.

The remaining two children in the convulsive group were so unresponsive as to be below test limits both before and after surgery.

Considering this sample in its entirety, the individual findings may be summarized as follows: One child showed a significant increase in rate of mental growth (over 10 points in I.Q.) following the c-j-a operation. Another child showed a significant decrease in rate of mental growth. Two severely epileptic children presented a more alert appearance, but there was no measurable improvement in intellectual ability at the time of repeat testing (one month and three months after surgery). Two spastic children gave evidence of fluctuating I.Q.'s (one increased 10 points and the other decreased eight points) but not in excess of normal expectancy for repeat psychometric testing. In the remaining 27 cases, there was no evidence that the rate of mental development had undergone any significant change.

Another way of examining the data is in terms of a group comparison preoperatively and postoperatively. It is possible that I.Q. changes which are too small to have individual significance might be sufficiently consistent to indicate a significant trend for the group as a whole. However, the average I.Q. change following surgery (in the 29 cases with measurable I.Q.'s both before and after the operation) was slightly minus (-1.8). This change is not significantly different from zero, according to the t-test of statistical significance.

General Discussion

1. Problems of Evaluation of "Intellectual Changes": Efforts to "raise intelligence" by psychologic and/or organic means have been legion in the 30 years that have passed since the introduction of the concept of the intelligence quotient. The improvement in mental level brought about by thyroid treatment in cases of hypothyroidism is an ex-

ample of the intellectual improvement that results from correcting the cause of the mental deficiency. It is but natural, therefore, that any theory of the etiology of a particular mental retardation (e.g., birth lesion) should lead by the shortest possible route to theories of how such deficiency may be modified.

However, the evaluation of various attempts to improve I.Q. has been difficult in the past and subject to a wide divergence of opinion. The same problems that beset previous researchers in this field confront present-day investigators in their efforts to evaluate the effect of the c-j-a operation upon intellectual status. The mere fact that a child is performing some activity, such as talking or walking, which he did not do prior to the operation, does not provide evidence that the operation was the cause of the improvement. Almost all mentally deficient children continue to make some progress, although at a slow rate, until puberty. The seemingly sudden appearance of a new ability is not unusual, even for normal children. Below the age of 3 years, the growth curve characteristically consists of sudden spurts followed by plateau periods. The natural tendency of parents to report some legitimate sign of improvement serves to confuse the picture. The crucial question is whether the improvement exceeds that which might normally be anticipated from the original quotient between the chronologic and mental ages, the I.Q., which represents the average rate of mental growth since birth.

In addition, it is necessary to appreciate the imperfections of the intelligence test as a measuring instrument. The probable error of the Stanford-Binet is approximately 5 points; this means that one child out of 5 may deviate as much as 10 points upon retesting. Also, the composition of the tests changes from the preschool-age levels to the school-age levels so that more weight is given at one age level than at another to a certain type of mental functioning. For instance the tests for children below the age of 2 years rely almost entirely upon feats of neuromuscular functioning. The ability to talk becomes a significant test factor at about 2 years, and gradually reasoning ability enters into the test picture.

Factors in administering the test should also be taken into consideration. All test subjects are influenced by the mood of the particular test situation and by their feeling for the examiner. Below the age of 6 years or so, a "good" psychologic test is obtained only if the child wishes to please the examiner; after school age, most children have a greater desire to do well for their own sake. Obviously, such factors should be considered in interpreting any test results that are obtained while a child is a patient in a hospital. In such circumstances the child's attention may be poor because of apprehension as to what may be coming next in the way of needles, etc., and the desire to please may be minimal because of feelings of being deserted.

Experimental studies on the constancy of the Stanford-Binet[3] have revealed that although "the Revised Stanford-Binet Scale is as good or better than any other objective index in predicting the future intellectual functioning of a preschool child . . . an individual I.Q. obtained prior to the age of six years must be interpreted with discretion." Thus, for both theoretic and empiric reasons, the use of changes in I.Q. to evaluate the effect of surgical, medical or psychologic intervention should be undertaken with caution.

2. Problems of Prognosis in Mental Deficiency: For practical purposes, mental deficiency may be defined as intelligence below a certain I.Q. (usually 65 or 70), but this single criterion does not determine whether a child will be deficient as a functioning unit in society when he becomes an adult. Doll of the Vineland Training School[4] makes this point clear in his differentiation between "feeble-minded" and "mentally deficient." The

former term he reserves for the socially incompetent who are, in addition, mentally deficient; it is his opinion that this diagnosis cannot be made prior to maturity, except in extreme cases.

Although the I.Q. is a useful concept in order to compare children of different chronologic ages, it is more useful to consider the mental age in looking ahead to the child's future as an adult. A mental age of five years is generally a prerequisite for the simplest kind of employment. Public schools, at least in metropolitan areas, provide training for children with this minimum mental age, although the I.Q.'s may range as low as 35. The future for these individuals is dependent upon many other factors besides intelligence. The coexistence of physical disabilities imposes additional limitations and obstacles. Family circumstances may improve a child's ability to function (if not his actual intelligence) by offering him special educational opportunities, affording him security and affection, and accepting his limitations. The child's capacity to control his instinctual impulses is an extremely important factor in determining whether he can adjust to an adult society. It is therefore erroneous to predict a certain achievement as denoting the maximum future possible for a child with a given I.Q.

Summary and Conclusions

The psychologic findings on 33 children following the c-j-a operation have been reported. The results show that almost all the patients improved in mental age but only at the same rate, in comparison with the chronologic age, which was evident prior to the operation. There was one instance of significantly increased rate with an I.Q. improvement of 18 points, and one instance of significantly decreased rate with an I.Q. loss of 20 points. The average difference in I.Q. following surgery was slight and in a minus direction.

Certain sources of confusion in evaluating intellectual changes have been discussed. A change in I.Q. within 10 points sometimes occurs with repeated tests for no specific reason beyond the measuring error inherent in the intelligence test. The mere fact of improved functioning in a child means little as far as evaluating surgical intervention is concerned, since most children are still in the process of growth, although it may be slow. Moreover, individual I.Q.'s obtained before the chronologic age of 3 years should be interpreted with discretion; this is particularly true in the case of spastic children who, in standard tests, are unfairly handicapped on a purely physical basis.

On the basis of the data reported in this study, the previous claim[1] that "this procedure represents the first successful attempt at correction of mental retardation on an organic basis" is not fulfilled. Although in previous reports by Beck, McKhann and Belnap, the concept of the I.Q. is used freely in general statements, no statistical facts have been provided. The improvement in two cases presented in the first published report by these authors has not been sustained by later study. The statement that children with I.Q.'s between 40 and 60 show the greatest improvement is contradicted by the present author's findings. There is virtually no evidence in this study (significant improvement in one case out of 33) for crediting the c-j-a surgical procedure with improvement of the intellect. The majority of the cases herein reported were tested several months after surgery so that whatever improvement was going to occur should have been manifest, according to the statement of McKhann, Belnap and Beck[2] that "improvement usually begins to appear in the retarded children within the first two postoperative months."

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REFERENCES

1. Beck, C. S., McKhann, C. F., and Belnap, W. D., Revascularization of brain through establishment of cervical arteriovenous fistula, J. Pediat. **35**:3, 1949.
2. McKhann, C. F., Belnap, W. D., and Beck, C. S., Cervical arteriovenous anastomosis in treatment of mental retardation, convulsive disorders and cerebral spasticity, Ann Surg. **132**:162, 1950.
3. Bradway, K. P., I.Q. constancy on revised Stanford-Binet from Preschool to Junior High School level, J. Genet. Psychol. **65**:197, 1944.
4. Carmichael, L., Manual of Child Psychology, New York, John Wiles & Sons, Inc., 1946, chap. 17.

SPANISH ABSTRACT

El Efecto de la Operacion Anastomosis-Carótida-Yugular Sobre la Inteligencia

Este estudio presenta las observaciones psicológicas que fueron hechas con respecto al estado intelectual de 33 niños antes y después de la operación anastomosis-carótida-yugular. La operación reportada previamente por Beck, McKhann y Belnap fué concebida para aumentar la circulación cerebral con la idea de mejorar las habilidades mentales de niños retardados especialmente seleccionados, así también como para obtener otros efectos benéficos, tanto en niños como en adultos. Estos pacientes recibieron pruebas individuales de inteligencia (Cattell y Binet) antes y después de la cirugía. El intervalo de tiempo entre la cirugía y la prueba postoperatoria fué de once meses. Los resultados mostraron que casi todos los pacientes mejoraron en edad mental pero únicamente al mismo ritmo en comparación con la edad cronológica, que fué evidente con anterioridad a la operación. Se encontró un paciente con un aumento significante en el índice de inteligencia (I.Q.) con una mejoría de 18 puntos, y otro con disminución significante en el índice de inteligencia (I.Q.) con pérdida de 20 puntos. La diferencia media en índice de inteligencia que siguió a la cirugía fue muy pequeña y en dirección negativa. Existe cierta confusión en evaluar cambios de inteligencia. El mero hecho de mejorar las funciones en un niño puede significar poco en lo que respecta a la evaluación de la intervención quirúrgica, tomando en consideración que la mayoría de los niños están aún en el proceso de crecimiento, aunque esto en algunos casos sea muy despacio. Sobre la base de los datos reportados en este estudio, no queda confirmada la frase de que "este procedimiento representa el primer intento satisfactorio de corregir el retardo mental sobre una base orgánica." La mejoría en los dos casos presentados en el primer reporte publicado por McKhann, Beck y Belnap no ha sido confirmada en estudios subsecuentes. Tomando este grupo como base, los resultados psicométricos encontrados para este grupo operado son los mismos que los reportados en otros estudios de niños de mentalidad deficiente en los que se hizo ningún intento terapéutico.

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PSEUDOMONAS AERUGINOSA INFECTION AS A COMPLICATION OF THERAPY IN PANCREATIC FIBROSIS (MUCOVISCIDOSIS)

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PAST studies[1-5] have shown the frequency of Staph. aureus infection of the respiratory tract as a complication of the defect in mucus-secreting glands observed in patients with pancreatic fibrosis (mucoviscidosis[6]). With prolongation of life in these patients as a result of increasing availability of antibacterial agents, it might be anticipated that infectious complications would not remain static or simple. Although other workers probably have had similar experiences,[7] the present investigators believe it significant to record observations of four consecutive patients with pancreatic fibrosis in whom Ps. aeruginosa was the predominant organism demonstrable in the respiratory tract. All these patients had received prolonged antibacterial therapy. A reconsideration of the bacteriologic findings and therapy is appropriate at this time in view of present recommendations for long continued antibacterial therapy in patients with mucoviscidosis and the potential emergence of a resistant bacterial flora in consequence of such therapy.

CASE REPORTS

Case 1: R. C. This male infant was first admitted to the Research and Educational Hospitals at the age of 14 mo. with a history of almost constant respiratory difficulty from the first week of life. He had been hospitalized elsewhere 4 times for episodes of bronchitis and bronchopneumonia and had received many courses of sulfonamides and penicillin both at home and in the hospital. In spite of a voracious appetite, he manifested marked growth retardation.

At the time of admission he was intensely cyanotic and dyspneic, and retractions were marked. The physical findings were those of an extensive bronchopneumonia, which was confirmed radiographically. Physical development was poor: the weight was only 6.0 kg. and the crown-heel length only 67 cm.

Stools lacked tryptic activity as evidenced by failure to digest gelatin. The succus entericus, obtained by duodenal drainage, gave no evidence of pancreatic enzyme activity, and the plasma amino acid nitrogen failed to increase significantly following calcium caseinate ingestion. Pancreatic fibrosis was diagnosed.

Bronchoscopy was performed 18 times during 7 mo. of hospitalization, both to remove secretions and to study the bacterial flora. He received antibacterial therapy almost continuously during this time. The order and duration of therapy was as follows: penicillin intramuscularly and by aerosol for 11 days; triple sulfonamide mixture (sulfadiazine, sulfathiazole, sulfamerazine) for 24 days; streptomycin by aerosol for 31 days; penicillin intramuscularly and by aerosol for 17 days; streptomycin intramuscularly and by aerosol for 17 days; polymyxin intramuscularly for 18 days; polymyxin by aerosol for 5 days; aqueous zephiran 1:1000 by aerosol for 21 days; and aureomycin by mouth for 36 days. There was some overlapping of these courses of therapy.

During the first 13 days of hospitalization, the patient's nasopharyngeal cultures contained no Staph. aureus or other pathogens. By the 14th day, after continuous penicillin therapy, a moderate growth of Ps. aeruginosa was obtained from the pharynx in the absence of other pathogenic bacteria. The organism was likewise obtained from bronchial secretions. Thereafter, Ps. aeruginosa was persistently present as the predominating organism in the nasopharynx and bronchi during the

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succeeding 6 mo. in spite of all therapeutic efforts to eradicate it. Most frequently it was associated with A. aerogenes, and inconstantly a coagulase-positive, hemolytic Staph. aureus or alpha or gamma streptococcus was found. At times pseudomonas was isolated in pure culture. *In vitro* studies revealed that this organism was not sensitive to aureomycin 25 units/cc. When no growth occurred after exposure to a 1:1000 aqueous zephiran solution for 1 min., this agent was chosen for therapy and was given by aerosolization, but the bronchial secretions continued to show a heavy growth of Ps. aeruginosa during therapy.

During the course of hospitalization, the patient improved markedly, as judged by weight gain and improved neuromuscular development, though he continued to have coughing paroxysms. When his improvement became static, he was discharged to his home environment on panteric granules ® and a dietary regimen 7 mo. after his admission.

The patient later died at a hospital in his home community approximately 1 yr. after he was first seen by the authors. No data were available regarding his bacteriologic flora at that time. Sections of his pancreas were sent to this department of pathology, and the diagnosis of pancreatic fibrosis was confirmed.

Case 2: P. O. This white girl was admitted to the Research and Educational Hospitals for the first time at the age of 5½ yr. She had first developed a cough on the 8th day of life and had had episodes of bronchitis frequently thereafter. She was finally diagnosed as having pancreatic fibrosis at the age of 2½ yr. Antibacterial agents in the form of sulfonamides and penicillin were administered on numerous occasions during this early period of her life. At the age of 3½ yr. duodenal drainage was performed which was said to have contained a decreased amount of trypsin, though actual values were not available. Two years before admission, she was maintained on continuous courses of penicillin (intramuscularly and by aerosolization) alternating with sulfamerazine. When streptomycin became available, it was combined with penicillin and administered by aerosol on several occasions. In the last 6 mo. before admission, this program had been discontinued, and the child had received only two 10 day courses of aureomycin.

Three weeks prior to admission, the child developed paroxysmal coughing, progressive dyspnea and intermittent cyanosis. Cyanosis soon became constant except when she was in a highly oxygenated atmosphere. She was admitted to the hospital in a critical state. Her digits were clubbed. The chest had an emphysematous configuration. There were marked retractions of the soft tissue portions of the thoracic wall. She was cyanotic and had evidence of right heart failure as manifested by facial and periorbital edema. The liver was palpable in the midclavicular line 5 cm. below the right costal margin. The pulse was 140. The child was restless, intermittently disoriented and unable to cooperate in diagnostic or therapeutic procedures. Her cough was loose but seemed to be entirely ineffectual in raising secretions. The rectal temperature was 37.0° C.

On the day of admission bronchoscopy was performed. The aspirated secretions were grayish-yellow in color and almost completely filled the trachea and major bronchi. Their tenacity was such that removal was incomplete, and the bronchoscopy was a therapeutic failure. A marked respiratory acidosis was present. The carbon dioxide combining power of the plasma was 46 mEq./l. and attested to the severity of the interference with respiratory exchange. On the second hospital day tetanic manifestations appeared. Bronchoscopy was repeated with no additional success, and a tracheotomy was performed to aid in the aspiration of secretions on the ward. All attempts at therapy were unsuccessful, however, and the child became exhausted from her respiratory efforts and died in respiratory failure approximately 24 hr. after admission.

Streptomycin and penicillin were given intramuscularly from the time of admission, and chloramphenicol was begun on the second day. Culture of the first bronchial secretions yielded many colonies of Ps. aeruginosa, a few N. catarrhalis, P. morganii and gamma streptococci. The secretions obtained at the time of the second bronchoscopic aspiration gave only a pure culture of Ps. aeruginosa. Blood culture was negative. Postmortem findings revealed pancreatic fibrosis, suppurative bronchitis and bronchiectasis with multiple pulmonary abscesses. The purulent material, both within the tracheobronchial tree and the pulmonary abscesses, yielded a pure culture of Ps. aeruginosa.

Case 3. C. W. This white girl was admitted to the Research and Educational Hospitals for the first time at the age of 2 yr. She had been in fairly good health for the 1st 5 mo. of life except for gastrointestinal disturbances. Respiratory infection then developed, and a chronic cough became part of the symptomatology. Repeated bouts of pulmonary infection occurred thereafter. Though no exact record of antibacterial therapy was available, it was presumed to have been extensive, for

many physicians had been consulted. Rectal prolapse frequently complicated the paroxysms of coughing. Her slow physical and neuromuscular development was considered symptomatic of her illness. She was first diagnosed clinically as a case of pancreatic fibrosis at the age of 18 mo. and was given pancreatin thereafter.

Three days before admission to the hospital, the child developed a heavy, greenish-yellow nasal discharge, paroxysmal coughing with an inability to raise secretions, dyspnea, cyanosis and excessive sweating. She was given penicillin during this time at home. When observed by the authors, she was desperately ill, malnourished, pale and cyanotic. She was restless and responded poorly. Her pulse rate was 160, and the muscles of her extremities were hypotonic. Retractions and marked dyspnea were present. Temperature was 38.0° C. rectally.

Bronchoscopy was performed on the day of admission for the aspiration of secretions. A thick tenacious material, too viscid for removal, could be seen exuding through the larynx. The child became comatose, developed increasing facial edema as a manifestation of right heart failure, and finally carpo-pedal spasm appeared with respiratory acidosis. All therapeutic efforts failed, and the child died in respiratory failure less than 30 hr. after admission.

The patient received penicillin by aerosolization and intramuscularly during her hospital course along with streptomycin intramuscularly. The culture of nasopharyngeal secretions yielded a heavy growth of Ps. aeruginosa and a few pneumococci unidentified as to type. At postmortem the diagnosis of pancreatic fibrosis was confirmed histologically. A suppurative bronchitis was present. Purulent viscid secretions formed a complete cast of the tracheobronchial tree, and a pure culture of Ps. aeruginosa was obtained from this material.

Case 4. C. B. First Admission: This white boy was first admitted to the Research and Educational Hospitals at the age of 4½ yr. An older sibling had died of proved pancreatic fibrosis, and a younger sibling, 3 mo. of age, had no trypsin in his stools but was asymptomatic at the time.

The patient had been well until 6 wk. of age. He then had experienced recurrent bouts of pneumonitis. It was not until he was 2 yr. of age and had an especially severe episode of pneumonitis accompanying rubeola, however, that he was diagnosed as having pancreatic fibrosis. Subsequently, he was maintained on pancreatin, dietary regulation, and frequent courses of chemotherapy and antibiotics. He attained his maximum weight 6 mo. prior to the present admission when he weighed 15.9 kg. at the age of 4 yr.

During the 5 mo. preceding his first admission to this hospital, his course had been progressively downhill with fever and weight loss despite a voracious appetite. He had a persistent, hacking cough, and had been treated with several courses of penicillin and aureomycin. Two weeks previous to his hospital admission he developed progressive dyspnea and cyanosis.

On admission his temperature was 40.3° C., pulse 140, respirations 56. There were marked retractions of the soft tissue portions of the thoracic wall. The chest was emphysematous in appearance, and a pigeon-breast deformity and moderate Harrison's grooves were present. WBC count was 19.0 thousand/cmm. Radiographic studies of the chest revealed diffuse bronchopneumonia bilaterally and partial atelectasis of the right middle lobe. The changes on roentgenogram persisted later even though clinical improvement occurred. The degree of respiratory acidosis was partially indicated by a carbon dioxide combining power of 38 mEq./l.

The patient's stools failed to digest gelatin, trypsin was absent in the succus entericus, and there was no rise in the plasma amino acid nitrogen after casec ingestion. Thus the diagnosis of pancreatic fibrosis was confirmed clinically.

The initial culture of nasopharyngeal secretions yielded no pathogenic organisms; however, penicillin was administered to the child both intramuscularly and by aerosol from the time of admission. Four days later a sputum specimen obtained on deep coughing yielded a heavy growth of Ps. aeruginosa. *In vitro* sensitivity studies of this organism revealed that it was insensitive to streptomycin 25 units/cc. The organism was also insensitive to terramycin 12.5 units/cc. In spite of the *in vitro* results streptomycin, both intramuscularly and by aerosol, was added to the penicillin therapy for 13 days. Terramycin was also added later and given orally for 13 days. During the last 7 days in the hospital, the child received chloramphenicol. Penicillin was continued throughout. The child was bronchoscoped 6 times during his hospital stay. On the 1st 2 occasions secretions obtained were not cultured. The last 4 times, however, pure cultures of pseudomonas were grown from the bronchial secretions; on one occasion an associated coagulase-positive Staph. albus was also found.

During the last 10 days of the child's 43 day hospital stay, he was ambulatory, afebrile, cheerful and almost free of cough in spite of his persistent pseudomonas infection.

Second Admission: One month following the first admission, the child was rehospitalized for 3 days for bronchoscopic aspirations. He had at this time a recurrent cough and increasing dyspnea. Bronchial secretions again revealed many Ps. aeruginosa organisms. A few coagulase-positive, hemolytic Staph. aureus organisms were also found along with very few gamma streptococci. The child had been receiving aureomycin from the family pediatrician for several days prior to this admission.

Third Admission: Twenty-four hours after the second hospitalization, the patient became markedly dyspneic and cyanotic and appeared to be in a terminal state. He was re-admitted and bronchoscoped on 2 further occasions with the same bacteriologic results noted at the previous hospitalization. Penicillin and aureomycin were given. The patient, however, died in respiratory failure 8 days following this admission.

Postmortem examination confirmed the diagnosis of pancreatic fibrosis and revealed an acute and chronic bronchitis, bronchiectasis and bronchopneumonia. Unfortunately, no cultures were obtained directly from the lungs at this time. The cardiac blood was sterile.

Discussion

The preceding case reports illustrate the effect of prolonged antimicrobial therapy in altering the flora of the tracheobronchial tree. Susceptible organisms apparently were eliminated by therapy, but Ps. aeruginosa, manifesting a high degree of antibacterial resistance *in vivo,* persisted and was eventually associated with the terminal episode in at least 3 of the 4 cases.

The concept of a changing bacterial flora during antibiotic therapy has now been described many times in the medical literature. Lipman, Coss and Boots[8] in 1946 studied the bacterial flora of the throat in 10 patients with rheumatoid arthritis who were given large doses of penicillin orally over a period of months. Gram-positive organisms predominated in the throat prior to therapy in each patient, and coliform bacteria were absent. During therapy there was a change to a gram-negative flora. Coliform organisms appeared early and often predominated throughout the course. Haffner et al.[9] studied the flora of the upper respiratory tract in 90 children treated with penicillin alone or in combination with sulfonamides. In a high percentage of these children a predominant gram-negative flora developed where no gram-negative organisms had been present prior to treatment. The bacteria encountered in the patients who "converted" included members of the E. coli-A. aerogenes group, A. fecalis, K. pneumoniae, and Ps. aeruginosa. Four children in this group died and were autopsied; 3 of these 4 had lung infections with gram-negative bacteria.

Weinstein[10] has directed attention to the danger associated with a shifting bacterial flora during antibiotic therapy. Thus 2 of 9 cases of influenzal meningitis which he treated with streptomycin developed bronchopneumonia and bacteremia due to Staph. aureus at a time when they were still under therapy and were apparently recovering from the meningitis. A third patient in the series died of an intercurrent Staph. aureus bronchopneumonia. Weinstein[11] later reported the overgrowth of H. influenzae in the throat of a patient receiving penicillin; the change was followed by pneumonia and septicemia due to that organism. A second patient developed a Friedländer's bacillus pneumonia while receiving penicillin for the treatment of faucial diphtheria. These new infections occurring during antibiotic treatment are sometimes referred to as "superinfections."[12]

Ps. aeruginosa has been particularly incriminated as an organism which is initially resistant or readily acquires resistance to all available forms of antibacterial therapy. This resistance renders it a potential hazard as a superinfection during antibacterial therapy. Frank, Wilcox and Finland[13] reported the *in vitro* sensitivity of Ps. aeruginosa (and B. proteus) to seven antibiotics: penicillin, polymyxin, aerosporin, aureomycin, chloramphenicol, streptomycin and bacitracin. The pseudomonas organisms tested were virulent strains

recovered from infected urine, sputum, wounds and exudates. The authors concluded that this bacterium is highly resistant to the antimicrobial agents generally used at the present time and that it frequently persists or replaces infections with susceptible organisms when such therapy is used. Penicillin and bacitracin were completely ineffective *in vitro*. Aureomycin and chloramphenicol were inhibitory for most strains but only in concentrations impossible to attain *in vivo*. Streptomycin was effective in moderately high concentrations, but a significant proportion of the organisms were highly resistant initially. Aerosporin had the most marked inhibitory effect followed by polymyxin. The difficulties in the clinical use of these latter antibiotics are well appreciated.

Alexander[14] refers to Ps. aeruginosa as an organism which readily develops resistance because of the numbers of resistant cells which may be present initially. Ps. aeruginosa, isolated from human infections, has been shown to vary considerably in the morphologic appearance of its colonies, and there is evidence that dissociation of the organism may occur *in vivo* as well as *in vitro*.[15] Insofar as this dissociation represents a high rate of bacterial mutation, it may be correlated with a high degree of resistance to antibiotics.

Experimental evidence reported by Demerec[16, 17] now indicates that bacterial resistance for a given antibiotic agent follows a pattern arising from the genetic mutation of bacterial cells. Naturally occurring resistant mutants are present in all large bacterial populations and have a continuous random occurrence.[14] These mutants breed true. Antibacterial agents lead to their selection by the destruction of susceptible bacteria. If bodily defensive mechanisms are unable to cope with the remaining mutants, a predominant resistant strain may emerge. Prolonged therapy with a single antibiotic agent increases the opportunity for the development of these resistant cells. Bacteria may even become so resistant to an antibiotic that they acquire a dependence upon it as a nutritional agent. Alexander and Leidy,[18] for example, have reported mutants of Ps. aeruginosa which require a tremendous concentration of streptomycin in the medium for growth. Prolonged administration of streptomycin in a patient having this strain could only make the infection worse.

At one time Ps. aeruginosa was considered to be a relatively harmless contaminant in bacterial cultures because of its lack of invasiveness. Stanley,[19] however, in 1947 reported 10 cases and reviewed the literature giving an extensive bibliography of cases in which the organism produced various clinical infections. Reported cases included sepsis, endocarditis, meningitis, brain abscess, arthritis, osteomyelitis, corneal ulcers, otitis externa and media, and infections of the urinary and respiratory tracts. Kerby[20] in the same year presented a more limited review and found 90 cases of bacteremia due to this organism prior to his report. In the past, isolated case reports have appeared establishing Ps. aeruginosa as a pathogen without question. Infants, children, and debilitated adults have been described as the chief victims of such infections. The enlarging chemical and antibiotic armamentarium of the physician today has brought increasing clinical importance to the pseudomonas strain of organisms at all ages, however.

In the light of the foregoing discussion, it would appear desirable to examine critically the recommendations for antibacterial therapy which have been proposed for children with pancreatic fibrosis. In 1946 di Sant'Agnese and Andersen[5] recommended sulfadiazine during the stage of chronic cough, both for prophylaxis and for treatment of intercurrent infections. May and Lowe[21] later stated that "penicillin and/or streptomycin have been given by aerosolization and such therapy has been continued for from 6 weeks to 1 year according to the clinical response." Shwachman[4, 22] more recently has recommended the prophylactic use of aureomycin continuously for a number of months "with occasional

short periods of freedom." He reports that clinical improvement bears no relation to bacteriologic improvement and that "excellent to good" results were obtained in 45 of 50 cases.

These approaches to treatment undoubtedly are effective in early cases when Staph. aureus infections predominate, but are not in keeping with our present knowledge of the development of bacterial resistance and sound principles of antibiotic therapy. Any regimen of long-continued therapy with a single antibacterial agent invites the development of highly resistant organisms which may flourish in an environment rendered more favorable by the absence of susceptible bacteria. Superinfection would be expected to become a clinical problem under such regimens, as it did in the cases presented in this paper.

Continuous prophylactic antibiotic therapy thus appears open to question. Regardless of the pattern of resistance, long-continued therapy with the same agent will lead to the emergence of resistant strains, especially of Ps. aeruginosa and those bacteria possessing a high degree of resistance initially. Logically, therapy should be intermittent in patients with pancreatic fibrosis to prevent superinfections with resistant bacteria. Instead of the administration of a single antibiotic, as suggested by authors previously cited, the most effective antibacterial agents should be employed judiciously and changed when specifically indicated. Frequent culturing of nasopharyngeal material, or if possible, of tracheobronchial secretions, should determine the choice of antibiotics. The antibiotic should be discontinued as soon as the desired effect has been attained. To minimize the appearance of resistant strains combinations of two antibiotics having different mechanisms of action are probably desirable, and evidence to indicate that this may be true for Ps. aeruginosa both *in vitro* and *in vivo* has appeared recently.[23]

Summary

Four cases of proved pancreatic fibrosis in which Ps. aeruginosa was the organism associated with the terminal, bronchopulmonary manifestations have been presented. These children had received prolonged antibacterial therapy varying from one to five years.

Ps. aeruginosa, or similarly resistant organisms, which ordinarily have a low pathogenicity, may become predominant and invasive as a result of prolonged antibacterial therapy. The opportunity for the emergence of resistant strains would seem to be enhanced by recent recommendations advocating continuous antibacterial therapy with a single compound. Intermittent therapy, alternating the various antibacterial agents and correlating their use with careful bacteriologic studies of the nasopharyngeal and tracheobronchial flora, would seem to be the logical approach to treatment in the light of present knowledge of the development of bacterial resistance. Mixtures of two antibiotics having a different mechanism of action may be more desirable than the use of a single agent.

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References

1. Farber, S., Pancreatic insufficiency and coeliac syndrome, New England J. Med. **229**:653, 1943.
2. Andersen, Dorothy, Cystic fibrosis of pancreas and its relation to celiac disease, Am. J. Dis. Child. **56**:344, 1938.
3. Zuelzer, W. W., and Newton, W. A., Pathogenesis of fibrocystic disease of pancreas, PEDIATRICS **4**:53, 1949.

4. Shwachman, H., Crocker, A. C., Foley, G. E., and Patterson, P. R., Aureomycin treatment in pulmonary involvement of pancreatic fibrosis, New England J. Med. **241**:185, 1949.
5. di Sant'Agnese, P. E. A., and Andersen, Dorothy, Celiac syndrome. IV. Chemotherapy in infections of respiratory tract associated with cystic fibrosis of pancreas, Am. J. Dis. Child. **72**:17, 1946.
6. Farber, S., Some organic digestive disturbances in early life, J. Mich. State M. Soc. **44**:587, 1945.
7. Shwachman, H., Foley, G. E., and Cook, C. D., Aureomycin in pediatrics: Review, J. Pediat. **38**:91, 1951.
8. Lipman, M. D., Coss, J. A., and Boots, R. H., Changes in bacterial flora of throat and intestinal tract during prolonged oral administration of penicillin, J. Bact. **51**:594, 1946.
9. Haffner, F. D., Neter, E., and Rubin, M. I., Penicillin and its effect in producing predominant gram-negative bacillary flora in upper respiratory tract of children, PEDIATRICS **6**:262, 1950.
10. Weinstein, L., Treatment of meningitis due to Hemophilus influenzae with streptomycin, New England J. Med. **235**:101, 1946.
11. Weinstein, L., Spontaneous occurrence of new bacterial infections during course of treatment with streptomycin or penicillin, Am. J. M. Sc. **214**:56, 1947.
12. Appelbaum, E., and Leff, W. A., Occurrence of superinfections during antibiotic treatment, J.A.M.A. **138**:119, 1948.
13. Frank, P. F., Wilcox, C., and Finland, M., In vitro sensitivity of B. proteus and Pseudomonas aeruginosa to seven antibiotics, J. Lab. & Clin. Med. **35**:205, 1950.
14. Alexander, Hattie E., Origin of resistance of bacteria and therapeutic implications, PEDIATRICS **1**:273, 1948.
15. Gaby, W. L., Study of dissociative behavior of Pseudomonas aeruginosa, J. Bact. **51**:217, 1946.
16. Demerec, M., Origin of bacterial resistance to antibiotics, J. Bact. **56**:63, 1948.
17. Bryson, V., and Demerec, M., Patterns of resistance to antimicrobial agents, Ann. New York Acad. Med. **58**:283, 1950.
18. Alexander, Hattie E., and Leidy, Grace, Mechanism of emergence of resistance to streptomycin, PEDIATRICS **4**:214, 1949.
19. Stanley, M. M., Bacillus pyocyaneus infections, Am. J. Med. **2**:253 and 347, 1947.
20. Kerby, G. P., Pseudomonas aeruginosa bacteremia, Am. J. Dis. Child. **74**:610, 1947.
21. May, C. D., and Lowe, C. U., Treatment of fibrosis of pancreas in infants and children, PEDIATRICS **1**:159, 1948.
22. Shwachman, H., Progress in study of "mucoviscidosis," PEDIATRICS **7**:153, 1951.
23. Armstrong, C. W. J., and Larner, A. E., Effect of combinations of antibiotics on Pseudomonas aeruginosa and Proteus vulgaris: In vitro and in vivo, J. Lab. & Clin. Med. **37**:584, 1951.

SPANISH ABSTRACT

Infección a Pseudomonas Aeruginosa como Complicación del Tratamiento Empleado en la Enfermedad Fibro-Quística del Pancreas (Mucoviscidosis)

Se describen cuatro casos confirmados de enfermedad fibro-quística del pancreas en los cuales la Pseudomonas aeruginosa fué el organismo patógeno causal de las manifestaciones bronquiopulmonares terminales. Estos niños recibieron un tratamiento antibacterial prolongado que osciló entre uno y cinco años.

La Pseudomonas aeruginosa, ú otros organismos similarmente resistentes, los cuales ordinariamente poseen una patógenecidad minima, pueden volverse predominantes e invasivos como resultado de un tratamiento anti-bacteriano prolongado. La oportunidad de la creación de especies resistentes de bacterias, es mucho mayor debido a las recomendaciones recientes que aconsejan una terapeutica antibacteriana contínua con un sólo agente. Una terapeutica intermitente, alternando varios agentes antibacterianos y relacionando su empleo con estudios bacteriológicos cuidadosos de la flora naso-faringea y traqueo-bronquial debe ser la actitud lógica del tratamiento. A la luz de los recientes conocimientos del desarrollo de resistencia bacteriana, la unión de dos antibioticos de mecanismo de acción diferente puede ser mas eficaz que el uso de un sólo agente.

1819 West Polk Street

ISOLATED CERVICAL LYMPHOGRANULOMA VENEREUM IN A CHILD

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LYMPHOGRANULOMA venereum is uncommon in sites other than the genitorectal region and is rarely found in children. Of 388 cases diagnosed at Bellevue Hospital in the period from 1936 to 1945, Costello and D'Avanzo[1] found only one in which regions other than genitorectal were involved. This was in the submandibular tissues of an adult. Their youngest case was a girl of 10 years who had been raped. Other cases in children have been reported by Sonck,[2] Weinstock and Keesal,[3] Bona Tome,[4] Winge,[5] Pereira and Gil,[6] Banciu and Caratzali,[7] and Levy.[8] Levy summarizes 11 cases and suggests that the disease can be responsible for rectal or genitourinary symptoms. He states that the childhood type of infection differs from the adult in the frequency of isolated inguinal involvement in children as compared with rectal in adults, and that the site of the primary infection is usually in the region of the urethra, most of the cases being girls. Elitzak and Kornblith[9] state that children may become infected through contaminated articles and that rectal infection has occurred by means of contaminated enema nozzles. A less common mode of rectal involvement in children is by coitus perversus. Of interest is Sonck's report that in five childhood cases which showed rectal involvement, the parents also had the disease.

Cervical lymph node involvement is uncommon, and in a review of the literature the author found no reports of cervical adenitis in children caused by the virus of lymphogranuloma venereum. When cervical involvement does occur in adults the site of the primary lesion is usually the mucous membranes of the mouth (Jones and Rome,[10] Buschke and Curth,[11] Coutts[12] and David and Loring[13]). In all these reports, acts of sexual perversion were considered the usual mode of infection. The oral lesion may be extensive. Serious ulcerating lesions of the oral mucous membranes have been described by Bergstrand[14] and by these authors.

The case reported here is of interest because it is one of lymphogranuloma venereum of a solitary cervical lymph node in a 6 year old boy in whom no primary oral lesion was identified.

CASE REPORT

E. S., a 6 yr. old white boy, was admitted to the pediatric service of Grasslands Hospital complaining of a lump in the neck of 10 days' duration. There had been an episode of epistaxis at the onset of the appearance of the mass. The swelling regressed for a few days but a week before admission it again became prominent and tender but was unaccompanied by fever, pharyngitis or respiratory infection.

There was a past history of frequent ear infections, especially on the right. The last such episode had occurred 1½ yr. prior to this admission. The patient had been admitted to Grasslands Hospital for scabies at 2 yr. of age and for tonsillectomy and adenoidectomy at 4.

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Physical examination revealed a well-developed and well-nourished boy who did not appear ill. There was a 2.5 by 3 cm. swelling on the right side of the neck anterior to the sternomastoid muscle and displacing it laterally and posteriorly. There was no erythema, fluctuation or fixation to the skin. Temperature was 37.8° C. The ear drums were scarred and retracted. There were shotty cervical, axillary and inguinal lymph nodes. The spleen was palpated 3 cm. below the costal margin. RBC count was 5.6 million/cmm. and the Hgb. was 13.5 gm./100 cc. (Sahli). WBC count was 13.7 thousand/cmm. with 67% neutrophilic leucocytes and 33% lymphocytes. Tuberculin tests using O.T. intracutaneously to a dose of 1 mg. were negative on 2 occasions. Erythrocyte sedimentation rate was 88 mm./hr. (Westergren). The reason for this marked elevation was not evident. Throat cultures were positive for alpha and beta streptococci. The blood contained no agglutinins

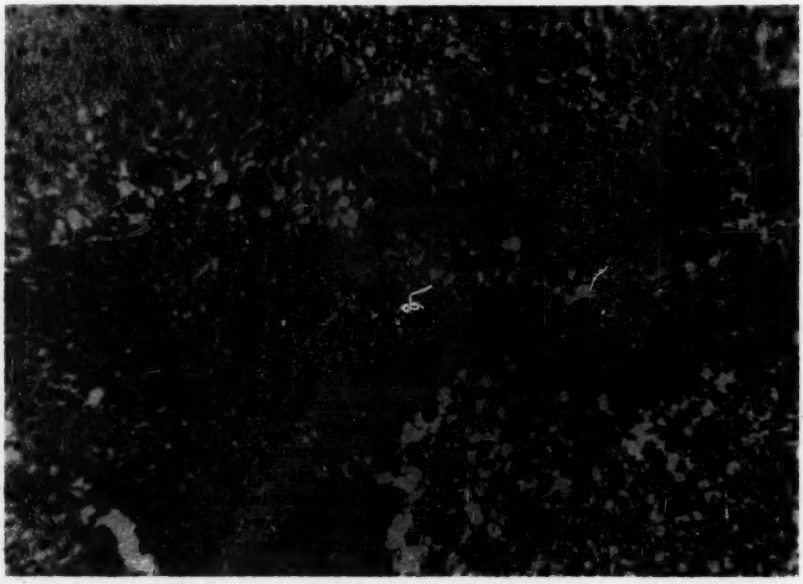

FIG. 1. Portion of stellate abscess, showing necrotic center and surrounding granulomatous zone. Note giant cell. (× 241 H. & E.)

for Brucella or Pasteurella Tularensis and the heterophile agglutination test was negative. The Wassermann reaction was negative. Sternal marrow punctures showed a slight increase in myeloid cells. Roentgenograms of the skull, long bones and spine were negative.

A course of penicillin, 100,000 u. 3 times daily for 10 days, had no effect on the size of the mass, which was growing slowly. Aspiration of the mass revealed sanguineo-purulent material which was negative on culture. Cultures for acid-fast organisms were negative. A smear showed only purulent exudate. Another course of penicillin, 200,000 u. twice daily, was ineffective. Three weeks after admission the mass was excised. Pathologic report was as follows:

Gross: The specimen consists of an irregular lobulated mass measuring 6 × 3 × 3 cm. It is encapsulated but covered with hemorrhagic adhesions. On section the cut surface is pink and traversed by fibrous strands. There are several cavities filled with creamy liquid.

Microscopic: Section shows a lymph node containing discrete, irregular abscesses, some of which have a stellate configuration. Within the abscesses are masses of necrotic neutrophilic leucocytes. Surrounding them are palisaded aggregates of epithelioid phagocytes, some of which are multinucleated. Beyond this zone the stroma is fibrotic and diffusely infiltrated with plasma cells, lymphocytes and some neutrophilic leucocytes. Acid-fast stain is negative. Staining with Machievello and Noble technics discloses intracytoplasmic inclusions within macrophages morphologically similar to the elementary and initial bodies of lymphogranuloma venereum (See Figs. 1-3.)

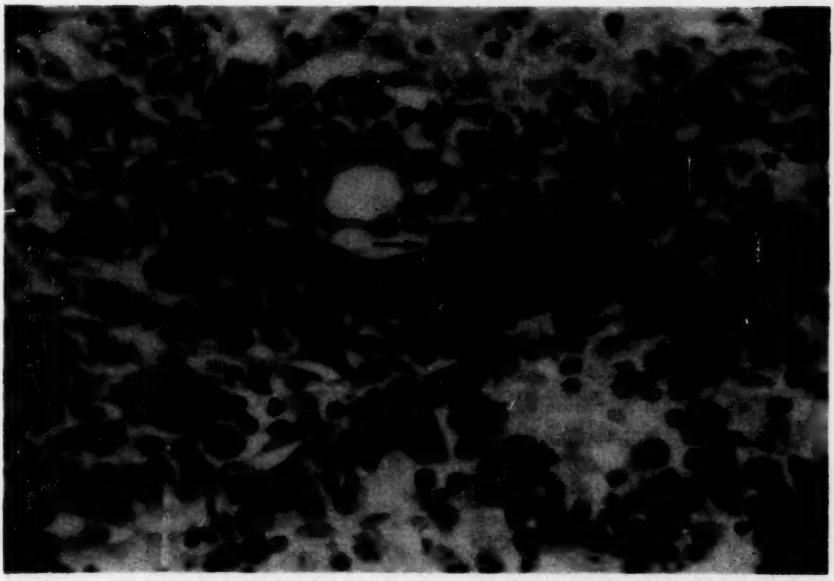

FIG. 2. Macrophage containing intracytoplasmic "elementary bodies." (× 453 Machievello stain.)

FIG. 3. Macrophage containing large intracytoplasmic "initial body." Cell nucleus has been compressed against thin rim of cell membrane by expanding inclusion. (× 727 Noble stain.)

Diagnosis: Lymphogranuloma venereum of cervical lymph node.

Fifteen days after excision a skin test using fresh Frei antigen derived from egg yolk resulted in a 4+ reaction. An egg yolk control was negative. The surgical wound healed rapidly and recovery was uneventful. A course of sulfadiazine was given for 1 wk., the dose being 0.12 gm./kg. and residual induration at the operative site disappeared. Follow-up examination 4 mo. later was negative. The parents (foster) and 2 siblings were tested with Frei antigen and found to be negative. No family or environmental history could be obtained suggesting a possible source of infection.

Discussion

The histologic picture in this case was consistent with that described by Sheldon and Heyman[15] who state that a reasonably characteristic picture presents itself in lymphogranuloma venereum and that a diagnosis may be made histologically. The morphologic appearance of the inclusions resembles that described by Findlay, MacKenzie and MacCallum[16] and by Rake and Jones.[17] Sheldon and Heyman mention that the typical inclusions occur only after necrosis appears in lymph nodes and are simply phagocytosed debris.

The Frei reaction is considered highly specific (Gelperin,[18] Anderson and Harmos[19]). However, Gray, Hunt, Wheeler and Blache[20] found that 50% of their series of positive Frei reactors in St. Louis gave no history of clinical lymphogranuloma venereum. Armstrong and Niebauer,[21] in their review of the literature, state that a false positive Frei reaction may occur when there is sensitivity to eggs. The egg yolk control in the case reported here was negative. On the other hand, Itikawa and Shinoda[22] report that in only 36% of the cases of lymphogranuloma venereum in their series had there been a demonstrable primary lesion. It is possible that many of the so-called false positive reactions occur in cases where overt clinical disease is not apparent but where subclinical infection exists.

It is now believed that lymphogranuloma venereum can manifest itself in various ways and that systemic infection may occur. Armstrong and Niebauer state that the disease may cause conjunctivitis, ophthalmitis, cystitis, liver abscesses, migratory polyarthritis and skin rashes. A case of atypical pneumonia due to the virus of lymphogranuloma venereum has been reported by Wood and Felson[23] and cases of meningoencephalitis have been reported by Sabin and Aring[24] and by Zarafonetis.[25] An interesting report by von Haam and D'Aunoy[26] describes an experiment in which the spinal fluid of eight patients with lymphogranuloma venereum, associated with fever and headache, was inoculated intracerebrally into mice. Two of the inoculations produced loss of weight and ataxia in the mice and when brain emulsions of these mice were used as Frei antigen in testing known human cases, a 4+ reaction resulted.

In the case reported here, the authors feel that the characteristic histopathologic changes combined with the positive Frei reaction are sufficient criteria for establishing a diagnosis of lymphogranuloma venereum.

Summary

A case of lymphogranuloma venereum manifested solely by involvement of a cervical lymph node in a boy 6 years of age is reported. The disease is uncommon in children and rare when the cervical region alone is involved.

References

1. Costello, M. J., and D'Avanzo, C. S., Lymphogranuloma venereum: Observations on 388 patients at Bellevue Hospital, Arch. Dermat. & Syph. **57**:112, 1948.
2. Sonck, C. E., Five cases of lymphogranuloma venereum in children, Acta dermat-venereol. **20**:171, 1939.

3. Weinstock, H. L., and Keesal, S., Lymphogranuloma venereum: Report of case in child, Urol. & Cutan. Rev. **50**:520, 1946.
4. Bona Tome, J. M., and Martinez, A., Un caso de linfogranulomatosis inguinal infantil, Actas dermo-sif. **32**:309, 1941.
5. Winge, M., Inguinal lymphogranuloma with special regard to occurrence in children, Nord. med. **9**:807, 1941.
6. Pereira, V., and Gil, J. B., Enfermedad de Nicolas-Favre en una nina de 18 meses, Arch. de pediat. d. Uruguay **12**:812, 1941.
7. Banciu, A., and Caratzali, A., Un cas de maladie de Nicolas et Favre a manifestations multiples, Ann. de dermat. et syph. **9**:100, 1938.
8. Levy, H., Lymphogranuloma venereum in childhood: Review of literature with report of case, Arch. Pediat. **57**:441, 1940.
9. Elitzak, J., and Kornblith, B. A., Lymphogranuloma venereum with rectal manifestations in child, Am. J. Dis. Child. **49**:703, 1938.
10. Jones, C. A., and Rome, H. P., Lymphogranuloma venereum as systemic disease, Internat. Clin. **2**:178, 1938.
11. Buschke, A., and Curth, W., Über die extragenitale Lokalisation des lymphogranuloma inguinale, Klin. Wchnschr. **10**:1709, 1931.
12. Coutts, W. E., Glossitis marginata in ihrer Beziehung zur lymphogranulomatosis inguinalis, Dermat. Wchnschr. **97**:1664, 1933.
13. David, V. C., and Loring, M., Extragenital lesions of lymphogranuloma venereum, J.A.M.A. **106**:1875, 1936.
14. Bergstrand, H., Can lymphogranuloma inguinale manifest itself as generalized disease with efflorescences in throat? Acta. oto-laryng. **12**:461, 1928.
15. Sheldon, W. H., and Heyman, A., Lymphogranuloma venereum: Histologic study of primary lesion, bubonulus, and lymph nodes in cases proved by isolation of virus, Am. J. Path. **23**: 653, 1947.
16. Findlay, G. M., MacKenzie, R. D., and MacCallum, F. O., Morphological study of virus of lymphogranuloma inguinale, Tr. Roy. Soc. Trop. Med. & Hyg. **32**:183, 1938.
17. Rake, G., and Jones, H., Studies on lymphogranuloma venereum, J. Exper. Med. **75**:323, 1942.
18. Gelperin, A., Specificity of Frei test in Army personnel using lygranum as antigen, Am. J. Syph. Gonor. & Ven. Dis. **27**:697, 1943.
19. Anderson, O. L., and Harmos, O., Lymphopathia venereum: Treatment with diluted Frei antigen intradermally and observations on its diagnosis, Surgery **3**:41, 1938.
20. Gray, S. H., Hunt, G. A., Wheeler, P., and Blache, O., Lymphogranuloma inguinale: Its incidence in St. Louis, J.A.M.A. **106**:919, 1936.
21. Armstrong, C. D., and Niebauer, J. J., Lymphogranuloma venereum: Review of literature with notes on 29 cases, Stanford M. Bull. **2**:107, 1944.
22. Itikawa, T., and Shinoda, R., Klinischke Beobachtungen uber Primarlasion von lymphogranuloma inguinale, Jap. J. Dermat. & Urol. **45**:79, 1939.
23. Wood, W. H., Jr., and Felson, H., Case of lymphogranuloma venereum associated with atypical pneumonia, Ann. Int. Med. **24**:904, 1946.
24. Sabin, A. B., and Aring, C. D., Meningoencephalitis in man caused by virus of lymphogranuloma venereum, J.A.M.A. **120**:1376, 1942.
25. Zarafonetis, C. J. D., Meningoencephalitis in lymphogranuloma venereum: Report of 2 cases, New England J. Med. **230**:567, 1944.
26. von Haam, E., and D'Aunoy, R., Infectivity of spinal fluid in lymphogranuloma venereum, J.A.M.A. **106**:1642, 1936.

SPANISH ABSTRACT

Linfogranuloma Venereo Localizado en un Solo Ganglio Cervical

Se reporta un caso de linfogranuloma venereo localizado a un solo ganglio linfatico cervical en un niño de seís años de edad. El diagnóstico se basó en el estudio histológico del ganglio y confirmado por una reacción positiva con el antigeno de Frei. La extirpación del ganglio, seguido por la quimoterapia aparentemente resultó en una curación completa.

Westchester County Department of Laboratories and Research

SOME OBSERVATIONS ON FACIAL PARESIS IN THE NEWBORN INFANT: ETIOLOGY AND INCIDENCE

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Galveston

EVEN today the etiology and incidence of the facial pareses seen commonly in the newborn infant are not completely known. These weaknesses are thought to be due to forceps trauma, except in the rare example of congenital aplasia of the seventh cranial nucleus.[1]

Two other origins of facial pareses are not generally considered in discussions of the etiology of this disorder.[1] The first group are those patients whose facial pareses are asso-

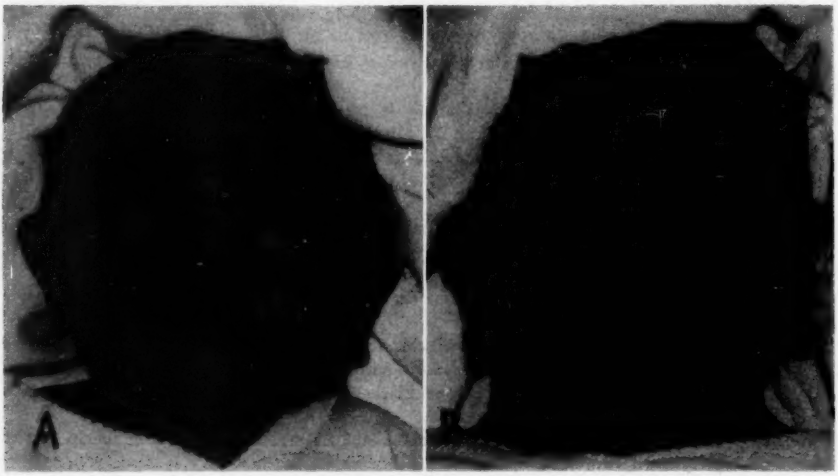

FIG. 1. This crying infant has facial asymmetry due to intrauterine posture. Right mandibular arch is flat; left is round. Right side of neck is less full than left. Open mouth exposes gums evenly. No forceps.

FIG. 2. This crying infant has facial asymmetry due to facial paresis. Mandible, ears and nose are symmetric. Open mouth exposes gums asymmetrically. Naso-labial fold on affected side is less curved. No forceps.

ciated with abnormalities of intrauterine posture.[2] Marked upward-inward displacement of the jaw and periaural portions of the head from strong pressure against the shoulder may result in sufficient pressure on the peripheral portion of the facial nerve to cause facial weakness. It is often difficult to differentiate facial weakness of this origin from

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asymmetry of the mouth made by upward and medial displacement of the mandible (see Fig. 1). Differentiation is dependent upon the actual movement of the lips in crying (see Figs. 2 and 3) rather than upon the oral asymmetry due to asymmetric opening of the lower jaw. Many newborn infants have the described asymmetry of the head and mandible, yet few have true facial paresis.

It is the remaining group that cannot be attributed to nuclear aplasia, intrauterine posture or forceps trauma to which attention will be directed here. These have been

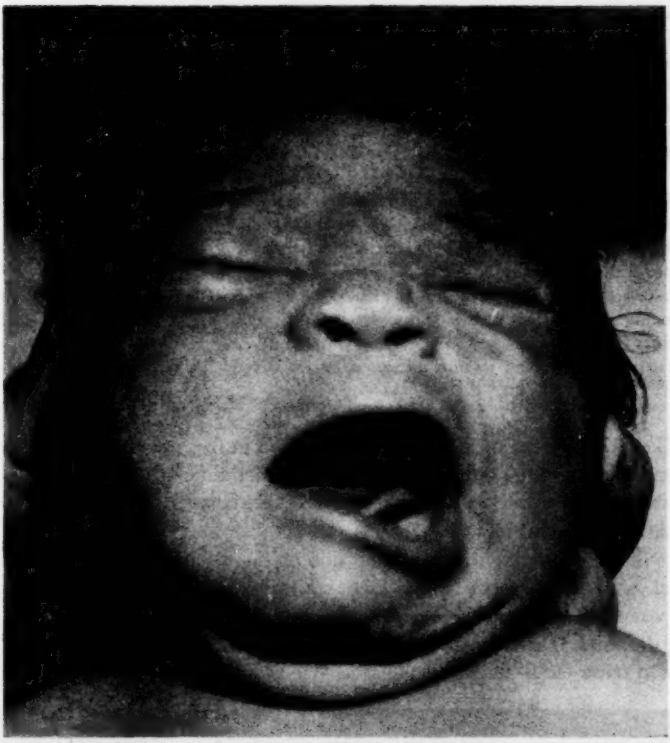

FIG. 3. This crying infant has facial asymmetry due to severe facial paresis. Naso-labial groove is absent on affected side. Mouth on affected side does not move. No forceps.

classified as "trauma due to intrapartum compression,"[1] and include those cases whose peripheral nerve damage is thought to be from compression against some maternal bony prominence, as the pubic rami, the ischial spines or the sacral prominence.[3, 4]

DATA

Infants of cephalic presentation from one thousand consecutive births were studied. All stillborn, breech births and premature births were eliminated in order that the conditions surrounding the births could be as standard as possible. There remained 875 mature infants, including 716 born with the aid of forceps, 159 born without the aid of forceps and 2 born by cesarean section after a test of labor. On the second day of life the infants were examined for evidences of facial pareses. (See table 1.)

TABLE 1

Type of Delivery	No. of Deliveries	No. of Facial Pareses	Incidence
Natural	159	10	6.3%
Forceps	716	46	6.4%

Among the 159 natural births, there were 10 infants with facial pareses (6.3%). The 6 infants who had left facial pareses were born from the obstetric position of occiput left transverse and, in all 6, external restitution was to the left. The 4 infants who had right facial pareses were born occiput right transverse and, in all 4, restitution was to the right.

Among the 716 forceps births, there were 46 infants with facial pareses (6.4%). Thirty-four infants had left facial pareses. All 34 were born from the obstetric position of occiput left transverse or anterior and, in all 34, external restitution was to the left. Twelve infants had right facial pareses. All 12 were born occiput right anterior, transverse or posterior, and all had external restitution to the right. In the two remaining infants there was no relation between the obstetric position and the side of facial weakness. One had a severe forceps mark at the angle of the jaw of the affected side, and the other had a marked postural depression of the appropriate side of the head with severe upward and inward displacement of the mandible and infolding of the ear as well as mild skin changes indicative of long-standing pressure. The shoulder point was flattened and exactly fitted the depression at the angle of the jaw.

The 2 cesarean births after a test of labor are of special interest. Both had facial pareses appropriate to the position of the occiput seen at delivery. Forceps were not used in either case. Both mothers had flat pelves.

No example of congenital seventh nucleus aplasia was found in this study.

Discussion

It is likely that the majority of facial pareses seen in the newborn infant are associated with intrapartum pressure on the exposed portion of the facial nerve, since the incidence of the disorder is the same in mature infants of cephalic presentation whether born with or without the aid of forceps.

The consistent association between the side of the obstetric position and the side of the facial weakness suggests an anatomic factor. Pressure against the spines of the ischium was not a factor in the two cesarean births, since the facial nerves did not cross the ischial spines. Then, by exclusion, since the maternal bony protuberance must be posterior to cause facial paresis on the same side as the obstetric position, the responsible

Fig 4. Anterior-posterior and lateral RGs of maternal pelvis before labor at term. Anatomic relationships shown here reveal opportunity for compression of fetal parotid region by prominence of sacrum during engagement and descent of head.

protuberance must be the prominence of the sacrum (see Fig. 4). During engagement and descent of the infant's head the facial nerve may be compressed by the sacral prominence in some instances. The mechanism described would be expected to occur more frequently in asynclitic[2] labors.

Summary

The incidence of facial paresis in 875 consecutive mature cephalic births was 6.4%. The use of forceps was found not to influence the incidence of facial paresis. Pressure on the sacral prominence during labor is probably responsible for the majority of facial pareses seen in the newborn infant.

References

1. Bonar, B. E., and Owens, R. W., Bilateral congenital facial paralysis: Review of literature and classification, Am. J. Dis. Child. **38**:1256, 1929.
2. Parmalee, A. H., Molding due to intra-uterine posture: Facial paralysis probably due to such molding, Am. J. Dis. Child. **42**:1155, 1931.
3. Geyl, Eine peripherische Facialisparalyse (Parese) bei einem Neugeborenen nach einer durchaus normalen Geburt, Zentralbl. f. Gynak. **20**:634, 1896.
4. Knapp, L., Fall von Facialisparese bei einem Neugeborenen nach spontaner Geburt, Zentralbl. f. Gynak. **20**:705, 1896.

Spanish Abstract

Observaciones en la Paresia Facial de los Recién Nacidos: Etiología e Incidencia

Se examinaron un total de 875 recién nacidos a termino, productos de partos normales con presentacion cefálica, para comprobar la presencia de paresia facial. La incidencia de paresia facial fué de 6.4%. Esta incidencia fué la misma tanto en los niños nacidos con ó sin la ayuda de forceps. De 159 niños nacidos sin aplicación de forceps, diez presentaron paresia facial, la cual estaba localizada en el mismo lado de la posición obstétrica del occipucio. De 176 niños nacidos con aplicación de forceps, 46 niños tuvieron paresia facial del mismo lado de la posición obstetrica del occipucio. Se estima que la espina del isquion materno puede desecharse como un factor causal, por presentarse paresia facial transitoria en niños nacidos por cesárea sin aplicación de forceps. La demonstración radiológica de la relación anatomica de la prominencia del sacro de la madre, y no el traumatismo del forceps, es probablemente responsable de la mayoria de las paresias faciales observadas en el recién nacido.

University of Texas—Medical Branch

MIDDLEBROOK-DUBOS HEMAGGLUTINATION REACTION

Study of the Test in Children

By H. W. ANDERSON, M.D., AND R. V. PLATOU, M.D.,
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UNTIL 1948, when Middlebrook and Dubos reported the hemagglutination of tuberculin-sensitized sheep erythrocytes by sera from tuberculous patients or animals,[1] there had been little or no success in the application of various serologic tests designed to define or measure activity of tuberculous disease.[2] In their original communication, these authors stated that the material active in this hemagglutination reaction was in the polysaccharide fraction of the tubercle bacillus, as indicated by the technic of specific inhibition of hemagglutination. Two reports have now appeared which attest a high correlation between positive reactions and activity of tuberculosis in adult patients.[2, 3]

Scott and Smith[4, 5] also pointed out that results of Middlebrook-Dubos tests are usually negative with sera from patients whose tuberculosis has been arrested for long periods, as well as from most patients with far advanced terminal forms of tuberculosis. They also noted that positive serologic tests may frequently be provoked simply by the antigenic stimulus of tuberculin testing in either positive or negative skin reactors, and that the possibility of either biologic false positive or negative serologic reactions has not yet been adequately studied. To date, leprosy is the only disease described in which this serologic test is frequently positive in the absence of tuberculosis.[6]

A frequent problem confronting the pediatrician is that of deciding whether a child who has a positive cutaneous reaction to tuberculin has active tuberculosis. Results of usual clinical studies to settle this point in a given patient are often equivocal and therefore cause understandable concern. It has been the present authors' practice in this dilemma to consider as tuberculous in origin all suspicious clinical, roentgenologic or other evidence of infection not proved to be due to other causes. Reasoning, then, that this hemagglutination reaction might be a useful adjunct in pediatric practice, the present studies were initiated. Given a positive Mantoux reaction—which does not differentiate between active, healing or healed disease—how should this newer test for humoral antibodies against tuberculosis be applied and interpreted?

PROCEDURE

The serologic procedure used in the authors' laboratory followed in every respect that outlined by Middlebrook and distributed as a memorandum to interested investigators in June 1950.[7] Three-hundred forty-three samples of serum were taken at irregular intervals from 287 children in the pediatric wards, general outpatient departments and tuberculosis clinics. After serologic results were

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TABLE 1

DISTRIBUTION OF ALL RESULTS IN MIDDLEBROOK-DUBOS TESTS AMONG 4 GROUPS OF PATIENTS

	Patient-Group			
	A	B	C	D
Mantoux	−	+	+	+
Clinical Activity	−	−	?	+
Serologic Results				
Negative	148	24	26	23
+, 1:2	24	7	8	5
+, 1:4	8	5	10	5
+, 1:8	1	8	10	8
+, 1:16	2	1	6	7
+, 1:32	1	—	1	1
+, 1:64	—	—	1	3
Total Sera	184	45	62	52
Total Patients	174	37	39	37

gathered, then pertinent data were taken from these patients' records as to epidemiologic, clinical, roentgenologic, bacteriologic and other laboratory evidences of tuberculous or unrelated disease; these were then set up against results of serologic tests for preparation of the tables and discussion which follow. Subsequently, all sera were considered in relation to their sources:

Group A: One hundred eighty-four were from sick or well infants and children who had negative Mantoux reactions and no other evidence of tuberculosis;

Group B: Forty-five were from those with positive Mantoux tests, but judged independently to have no other evidence of active tuberculosis (apparently benign primary infections);

Group C: Sixty-two were from those with positive Mantoux tests together with equivocal additional evidence of active tuberculosis such as recurrent or low-grade fever, slight or moderate in-

TABLE 1A

DATA OF TABLE 1, EXPRESSED PERCENTAGEWISE

	Patient-Group			
	A	B	C	D
Mantoux	−	+	+	+
Clinical	−	−	?	+
Serologic Results				
Negative or Positive 1:2	93.5	68.9	54.8	53.8
+, 1:4	4.3	11.0	16.1	9.6
+, 1:8	0.5	17.7	16.1	15.4
+, 1:16	1.1	2.3	9.6	13.4
+, 1:32	0.5	—	1.6	1.9
+, 1:64	—	—	1.6	5.8
Total, 1:4 or >	6.5	31.1	45.1	46.2

creases in leucocyte counts or erythrocyte sedimentation rates, indefinite evidences of pulmonary disease by physical or roentgenographic examination, etc.; about half the sera in this group were from patients judged to have satisfactory evidence of healing tuberculosis after therapy of active disease;

Group D: Fifty-two were from children judged to have definitely active tuberculous disease (miliary, meningeal, pulmonary or glandular).

All Mantoux tests were done with human-type old tuberculin prepared and used in accordance with manufacturer's directions.*

Patients ranged in age from 18 days to 12 yr., 198 of them being less than 6 yr. old, 40 less than 1 yr. old. The distribution as to race and sex among positive and negative cutaneous reactors to tuberculin was essentially similar; about 70% of the patients were Negro. Two or more serologic tests were completed for 52 patients; sera were drawn at intervals of from 1 day to 9 mo. following the application of skin tests.

Results

1. General.—In table 1, results of all serologic tests are set forth for each of the four groups of children. Previous reports[2, 3, 8] indicate that the presence of this humoral antibody in serum dilutions of only 1:2 probably has little or no significance. Accordingly,

TABLE 2

Serologic Results, from Patients of Group A, Related to Interval Between Negative Skin Tests and Collection of Sera

Result of M.D. Test	Interval from Date of Negative Mantoux, Days			
	1–7	8–30	31–60	>60
Negative	60	48	16	17
Positive 1:2	14	5	3	2
1:4	3	4	1	0
1:8	1	0	0	0
1:16	1	1	0	0
1:32	1	0	0	0
1:64	0	0	0	0
1:4 or >, per cent	7.5	8.6	5.0	0

in table 1a—where results appear percentagewise simply for the sake of easier comparison—the authors have chosen to consider tests positive only in this low titre along with negative results.

Inspection of these data reveals an apparent lack of selectivity or specificity of the serologic tests and raises several questions: Why did about 7% of sera from children with negative Mantoux reactions contain antibodies? Conversely, why did many children with positive skin tests (groups B, C and D) have negative serologic tests? What explanations might exist for these "unexpectedly" positive or negative serologic tests? Why should the distribution of positive serologic tests show variance among the three groups of children who had positive skin tests? How dependable is this test, when and how should it be applied, and how should it be interpreted? The remainder of this communication will be concerned with attempts to answer these questions.

2. Effect of Tuberculin Tests.—As would be expected, most (172 of 184) sera from

* Eli Lilly & Company, Indianapolis 6.

patients with negative skin tests contained little or no antibody. In table 2, serologic results are arranged according to intervals at which blood specimens were secured following most recent negative skin tests. It was of some interest to note that only 1 of the 39 patients whose sera were collected more than a month after skin testing had a positive test in a serum dilution greater than 1:2, and this one only in the next higher tube. These observations tend to confirm those of Smith and Scott,[5] indicating that the antigenic stimulus of a tuberculin test may be adequate in itself to provoke a positive serologic reaction.

All available data pertaining to each of the patients with negative Mantoux reactions but positive serologic tests were carefully scrutinized. No particular disease appeared to stand out as a cause for "false-positive" serologic tests: these were obtained in serum dilutions of 1:4 or greater with 12 specimens taken from 8 tuberculin-negative patients who had the following conditions: active rheumatic carditis (2 cases), idiopathic epilepsy, asthmatic bronchitis, typhus fever, acute pharyngitis, diphtheria or sickle cell disease. All

TABLE 3

SEROLOGIC RESULTS, FROM PATIENTS OF GROUPS B, C AND D, RELATED TO INTERVAL BETWEEN POSITIVE SKIN TESTS AND COLLECTION OF SERA

Result of M.-D. test	Interval from date of positive Mantoux, days			
	1–7	8–30	31–60	>60
Negative	9	10	4	50
Positive 1:2	3	5	2	10
1:4	1	7	4	8
1:8	7	8	2	9
1:16	3	1	1	9
1:32	—	—	—	2
1:64	2	1	—	1
1:4 or >, per cent	56	53	54	33

but one of these specimens were secured within a month of the time the tuberculin skin test was applied, and apparently the positive results were best explainable by a transiently provocative effect of these skin tests rather than by any particular disease. None of these 8 children was less than 3 years old; of the remaining children in group A, 35 were less than a year of age, and 48 were older than 6 years.

All eight tuberculin-negative children whose sera transiently contained antibodies in titers greater than 1:2 have been followed. None has developed any clinical evidence of tuberculosis and repeated skin tests, in doses up to 1.0 mg. of old tuberculin, have revealed no positive reactors. Because of repeated skin tests, evaluation of subsequent serologic results was difficult in these patients, as illustrated by the following example:

A 3 year old child with active rheumatic carditis had a negative skin test but a serologic test positive in a titer of 1:8. Retested in one week with 1.0 mg. of old tuberculin, the cutaneous reaction was again negative; seven days later the serologic titer was positive 1:2. Following a negative skin test with 1.0 mg. of old tuberculin again that same day, the serologic titer seven days later was 1:32.

Similarly irregular and confusing results were observed in the other seven patients who had negative skin tests followed by positive serologic reactions.

Results of serologic tests done at varying intervals following all positive tuberculin reactions appear in table 3; here it is apparent that there are more positive serologic tests than in the tuberculin-negative group, though again their proportion decreases with time. This, too, lends support to the contention that tuberculin provokes a rise in level of humoral antibodies, and this fact should influence interpretation of tests done with sera drawn during the first few weeks after skin tests are performed.

This apparently provocative effect of tuberculin testing is graphically portrayed in chart 1, which shows a transient rise in proportion of positive serologic tests in less than 10% of children who had negative skin tests. There is an apparently similar rise and

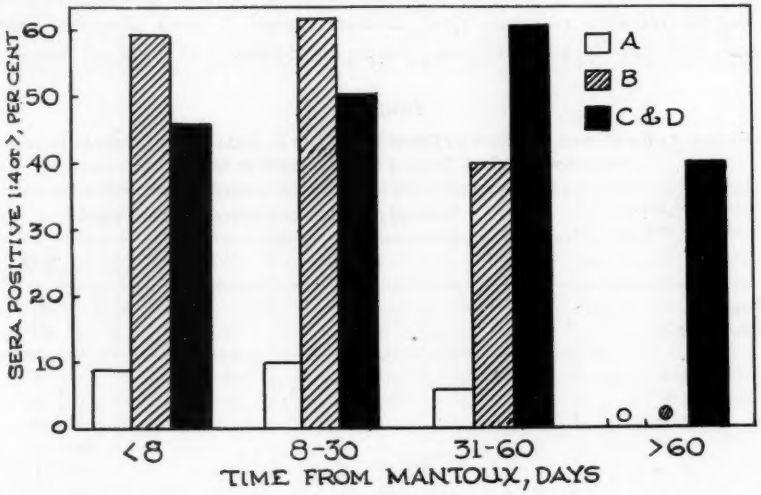

CHART 1. Changes in proportions of sera containing antibodies in dilutions of 1:4 or greater, related to time after skin tests. See text for definition of patient-groups A, B, C, and D.

fall in proportion of more frequently positive serologic results among children with positive skin tests (groups B, C and D). Beyond two months after Mantoux tests, no serologic titers higher than 1:2 were secured in children with presumably benign primary infections (group B); also, the proportion of noteworthy serologic titers from children with either questionable or obviously active disease (groups C and D) declined after 60 days.

3. Distribution of Serologic Results in Children with Tuberculosis.—Beyond the second month after tuberculin testing, none of the patients judged to have benign primary infections (group B) exhibited positive tests in serum dilutions greater than 1:2 (chart 1). The high proportion of this group having noteworthy levels of serum antibody soon after positive skin tests probably indicates an anamnestic response related to the duration of pre-existing tuberculosis or sensitivity to tuberculin. It is apparent, from the data of table 1 and of chart 1, that these children in group B with apparently benign primary infections exhibit a different serologic pattern from those in the other groups. It is equally apparent that patients in groups C and D seem to exhibit remarkably similar

TABLE 4

SEROLOGIC RESULTS, FROM PATIENTS OF GROUPS C AND D, WITH SPECIMENS SECURED 60 OR MORE DAYS AFTER POSITIVE SKIN TESTS

Serologic Results	Patient-Group			
	C		D	
	No.	Per Cent	No.	Per Cent
0–1:2	24	63	16	52
1:4 or >	14	37	15	48
Total	38	100	31	100

serologic responses—those with no more than equivocal clinical evidences of active tuberculous disease behaving serologically quite like those who have undoubtedly active tuberculosis.

Considering groups C and D together, results of serologic tests were then arranged in relation to race, various suspected or obvious reinfection types of tuberculosis, their estimated duration, and their presumed activity according to conventional clinical criteria; no correlations were apparent. It has previously been stated that a positive Middlebrook-Dubos reaction is frequently lacking or present in only low titer with sera from patients having far advanced terminal tuberculosis, and that there appears to be a decline in level of antibody with healing of tuberculous lesions in adults.[3,5,8] Among the authors' patients, there were only three judged to have terminal disease. These were all infants; five specimens of sera yielded completely negative tests. Insufficient data have been gathered to permit a positive statement concerning the significance of a single serologic result in any individual patient.

In table 4 appear proportions of low and high serologic results secured two months or more subsequent to tuberculin testing—when it was believed that most of the provoca-

TABLE 5

SEROLOGIC RESULTS, FROM GROUPS C AND D, RELATED TO STATUS OF DISEASE AND AGE OF PATIENTS
(Denominators represent total tests in each category; numerators indicate number positive in serum dilutions 1:4 or greater.)

Status of Disease	Age of Patients, Yr.		
	<1	1–6	6–12
Equivocal or Healing (C)	0/0	17/47	11/15
Terminal (D)	0/5	0/0	0/0
Active (D)	0/3	15/35	9/9
Total	0/8	32/82	20/24
Per cent	0	39	83

tive effect had been dissipated. After such an interval, there are fewer noteworthy serologic titers from children with equivocal clinical evidences (group C) than from those with obvious signs of active tuberculosis (group D). Still, more than a third of sera from children in group C contain elevated levels of humoral antibody; this might be taken to mean that the usual clinical criteria for judging activity of tuberculous disease are faulty, and that the Middlebrook-Dubos test may yet prove to be very helpful in settling such questionable cases. So far, at least, none of these patients originally classified in group C have developed obviously active reinfection forms of tuberculosis after intervals now extending for as long as eight months. On the other hand, it was gratifying to note that at least four of these 39 questionable patients, originally placed in group C, but having little or no humoral antibody two months after skin tests, could later be considered to have healed and inactive tuberculosis (group B).

4. Age Factor.—Results of serologic tests were then arranged in relation to age and status of all patients in groups C and D (table 5). Five negative sera of group D were from infants with terminal tuberculosis; 3 others from infants with active tuberculosis were also negative. Among children between 1 and 6 years of age, there were no cases of terminal disease, yet only 15 of 35 sera from this group contained antibodies in dilutions greater than 1:2. Twenty out of 24 sera from patients 6 to 12 years of age yielded tests positive in higher titers—and the only 4 patients in this group who had little or no antibody presented satisfactory evidences of healing tuberculosis.

Discussion

These observations, pending a larger experience, justify the following statements:

1. The Middlebrook-Dubos test may prove to be a useful addition to other technics directed at evaluation of tuberculous disease in children. Like all laboratory procedures, it has limitations—most of which appear to be predictable—requiring that results be interpreted in relation to the entire clinical picture.

2. Mantoux testing exerts a distinct but transient provocative effect on the level of humoral antibodies in a small proportion of both positive and negative reactors to the skin test. This effect is largely dissipated within a month or two. When clinical circumstances suggest the presence of tuberculosis in a given patient, it would be well to draw blood for serologic testing just before or at the time a tuberculin test is applied, to avoid possible confusion due to this occasional provocative effect.

3. Results of the serologic test are apt to be negative or only weakly positive in sera from children with obviously terminal tuberculosis, from those with apparently arrested or healing tuberculosis, and from more than half of those with questionably or obviously active tuberculous disease who are under 6 years of age. Thus, while a positive serologic test in a younger child may be meaningful, a negative serologic result is certainly not to be trusted in infants and younger children. Pending a larger experience, the authors believe that serial quantitative tests may nevertheless have considerable merit in supplementing other procedures used for evaluating progress of tuberculosis in young patients.

4. An age factor, conceivably only reflecting the duration of an individual's experience with tubercle bacilli, apparently is operative. This must be considered when one attempts to relate levels of this humoral antibody to other evidences of tuberculous disease. In view of the prompt rise of humoral antibodies after tuberculin tests in some older children, and the complete lack of antibody in sera from all the infants (35 in group A, 8 in group D), it seems likely that these immunologic differences are related more strictly

to age than to host experience with tubercle bacilli. It is of interest to note that most sera contain little or no humoral antibodies at the age when the incidence of serious disseminated tuberculosis is highest. Further therapeutic and prognostic implications which occur at once in relation to the importance of this apparent serologic deficiency in the youngest patients are outside the scope of this present communication.

Summary

The Middlebrook-Dubos hemagglutination test, measuring a humoral antibody against a polysaccharide fraction of the tubercle bacillus, has been studied in 343 sera from 287 infants and children. The test appears to be practical and may be useful as an index to activity of tuberculous disease.

A transient rise in level of antibodies was observed in some sera after either negative or positive skin tests with old tuberculin; this occasional provocative effect is largely dissipated within a month or two. Little or no antibody may be demonstrated in most sera from patients with either far advanced or healing tuberculosis. An age factor makes "unexpectedly" negative serologic results in most infants and younger children apparently quite meaningless.

References

1. Middlebrook, G., and Dubos, R. J., Specific serum agglutination of erythrocytes sensitized with extracts of tubercle bacilli, J. Exper. Med. **88**:521, 1948.
2. Rothbard, S., Dooneief, A. S., and Hite, K. E., Practical application of hemagglutination reaction in tuberculosis, Proc. Soc. Exper. Biol. & Med. **74**:72, 1950.
3. Rothbard, S., Serological test in tuberculosis, M. Clin. North America **35**:603, 1951.
4. Scott, N. B., and Smith, D. T., Simple modification of Middlebrook and Dubos hemagglutination test for serum antibodies to products of tubercle bacilli, J. Lab. & Clin. Med. **35**:303, 1950.
5. Smith, D. T., and Scott, N. B., Clinical interpretation of Middlebrook-Dubos hemagglutination test, Am. Rev. Tuberc. **62**:121, 1950.
6. Levine, M., Hemagglutination of tuberculin sensitized sheep cells in Hansen's disease (leprosy), Proc. Soc. Exper. Biol. & Med. **76**:171, 1951.
7. Middlebrook, G., Mimeographed instructions, distributed to investigators following ninth streptomycin conference held at St. Louis, April 18-21, 1950; Veterans Administration, Central Office, Streptomycin and Laboratory Committee, Washington 25, D.C.
8. Dubos, R. J., Hemagglutination test in tuberculosis: transactions of Ninth Streptomycin Conference, April 1950, pp. 222-223; Veterans Administration, Central Office, Washington 25, D.C.

Spanish Abstract

La Reacción de Hemoaglutinación de Middlebrook-Dubos; Un Estudio en Niños

La reacción de hemoaglutinación de Middlebrook-Dubos, determinando un anticuerpo humoral contra una fracción polisacárida del bacilo tuberculoso, ha sido estudiada en 343 sueros de 287 niños. La prueba parece práctica y útil como índice de actividad de la infección tuberculosa.

Un aumento transitorio en el nivel de los anticuerpos fué observado en algunos de los sueros después de resultados negativos o positivos en la prueba cutánea con tuberculina vieja; esta ocasional acción provocativa se disipa en su mayoría dentro de un período de un mes o dos. Poco o ningún anticuerpo se puede demostrar en el suero de enfermos padeciendo de lesiones avanzadas o en proceso de cicatrización. Un factor de edad hace los "inesperados" resultados negativos aparentemente insignificantes en la mayoría de los niños más jóvenes.

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CLINICAL SURVEY OF VASCULAR COMPLICATIONS IN "JUVENILE DIABETES MELLITUS"

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JUVENILE diabetic patients are well suited for the study of vascular disease in the peripheral and visceral blood vessels. At the onset there is no organic involvement of blood vessels, but as the diabetic state remains 10 or more years there occurs an increase in detectable vascular retinopathy, vascular sclerosis and renal vascular involvement.

The series presented here is small but the cases have been carefully and frequently followed over a period of years. The authors are prompted to present the results of their experience in order to help build a larger significant series.

METHODS OF STUDY AND ANALYSIS OF CASES

This survey consists of a study of 25 patients belonging to the so-called "juvenile type" of diabetes mellitus. Pertinent data regarding them is given in table 1. The factors considered and designated in this table are:

1. Present age
2. Age of onset
3. Duration of disease
4. Diet
5. Daily insulin requirements
6. Degree of control
7. Presence or absence of
   - retinopathy
   - periperal vascular calcification
   - renal involvement
8. Total blood lipids and cholesterol level

Only 2 patients were over 15 yr. of age at the time of onset of the disease. One was 16 yr. old and the other was 27. The duration of the disease in these 2 patients at the time of this study was 22 and 21 yr., respectively. The rest were under 15 yr. of age. Six of these 23 cases were 10 to 13 yr. old at the onset of the diabetes mellitus. The other 17 patients were 8 yr. of age or under.

The patients (with the exception of A. E. who came for treatment 3 yr. after diabetes developed) were all seen and treated by one of the authors at the time of onset of the disease. Treatment of the diabetes mellitus was continued without interruption except in 3 patients. These latter were seen at infrequent intervals during the past 3 or 4 yr. The rest were under close supervision, returning for examination every 2 to 8 wk., and a warm and personal relationship was established between physician and patient. As a rule, not only the diabetes, but all their illnesses were treated by the present authors, who were therefore fully acquainted at all times with their medical history and the state of control of the diabetes mellitus. Frequent check-ups also made it possible to determine the presence or absence of complications within a reasonably short period after their probable onset.

The authors' method of treatment underwent changes during the course of time (1925 to 1950). A single plan of treatment was never adopted. Treatment was always flexible, depending upon the personality and attitude of the patient, and the difficulties encountered in the management of the disease in each individual case. The authors never insisted upon a constantly normal blood sugar nor

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upon urine aglycosuric during the entire 24 hr. period. The latter was found impossible to attain without giving 3 to 4 daily injections of insulin and disregarding the occurrence of hyperinsulinism.

From the beginning the difficulties and the futility and unreasonableness of rigid adherence to a perfect control of glycemia and glycosuria were recognized. This was reported in an early paper.[1]

During the first insulin period, when only regular insulin was available, the use of 2 doses of regular insulin daily was recommended by the authors in practically all cases. In only a few, where it was felt important enough and where the patient permitted it, were 3 daily injections given. As a rule, all the patients excreted 10 to 30 gm. of glucose daily. Usually the maximum excretion was after breakfast and after retiring, or upon arising.

During the second period when protamine-zinc insulin was available, control of the diabetic state improved. Most of the patients still received 2 daily injections of insulin (protamine-zinc insulin and regular insulin either together or at different times). However, because of the use of high carbohydrate diets at the time, control was still far from satisfactory in that the patients excreted 10 to 20 gm. of glucose in the urine daily and their blood sugars were high during at least half of the 24 hr. period.

A change from the high carbohydrate diet was gradually made and wherever possible the patient was permitted a moderate intake of carbohydrates (200 gm. or less), a high protein intake (close to 100 gm.) and a fat intake of 100 gm. or less. Patients on this type of diet were easier to manage. They required lower doses of insulin and had practically no clinical evidence of hyperinsulinism.

With a 2 to 1 mixture (2 regular insulin units to 1 unit of protamine-zinc insulin combined), it has been possible to treat most of the cooperative patients on a single daily dose of insulin, which was much smaller than their previous combined dose.

A few patients have been maintained on a single dose of protamine-zinc insulin because they were under satisfactory control. Several others have not done well on this type of insulin therapy but have nevertheless refused to allow any change.

In the diet column in table 1 the usual dietary intake is described. A "plus" sign indicates that the subject took additional food on many occasions (3 or more times a week). "Free diet" signifies that the patient paid no attention to his caloric and carbohydrate intake and ate excessive amounts of food at all times.

The standards of control are not as rigid as those of Jackson and his colleagues.[2] They have been arbitrarily determined by the present authors on the following basis:

1. "Good Control" was applied to all cases where the blood sugar levels were normal or only slightly elevated during the greater part of the day and where the urine specimens were sugar-free or contained small amounts of sugar in some of the specimens. The daily glycosuria varied from 2 to 8 gm. In addition, except where acidosis occurred at the onset of the disease, there were no subsequent attacks of acidosis or coma, and infrequent attacks of clinical hyperinsulinism.

2. "Fair Control" was applied to those patients who showed significantly high blood sugar levels during 1 or 2 relatively short periods of the day, but no more than a total of 8 to 10 hr. a day. During the rest of the day they had normal or slightly elevated blood sugar levels. Their daily glycosuria varied from 10 to 20 gm. In this group, too, acidosis never occurred after the initial period of treatment.

Both the good and fair group showed great stability as far as their metabolism was concerned during a period of acute infection. At no time were more than the usual measures of therapy required for their illness. The only deviation that was found to be necessary was to administer their daily dose of insulin by means of 2 to 3 daily injections and this procedure was employed only during the active phase of the acute illness.

3. "Poor Control" is applied to the group with blood sugars moderately elevated to levels of between 200 to 300 mg./100 cc. during the greater part of the day. The glycosuria varied from 15 to 40 gm. or more/day.

4. "Very Poor Control" is applied to those who showed persistence of very high blood sugar levels (250 to 400 mg./100 cc.). The daily urinary excretion of glucose was 40 gm. or higher.

Only in the categories of poor or very poor control, was it found necessary to hospitalize patients on certain occasions, because of significant ketosis, acidosis or coma.

In evaluating degree of control, other factors beside blood sugar levels, glycosuria, frequency of acidosis and coma, were also taken into account, such as the patient's behavior during infection or during gastrointestinal disturbance, the frequency and character of attacks of hyperinsulinism, the

TABLE 1

Name	Age (Yr.)	Age (Yr.) at Onset	Duration in Yr.	Average Diet 10 yr.	Insulin	Degree of Control	Complications: Eye	Complications: RG Evidence of Vascular Calcification	Complications: Kidney	Blood Chemistry: Total Lipids and Cholesterol
Group I. Diabetes Duration 11–15 Yr.										
RB	17	6	11	CH—200 gm. P —100 gm. F — 70+	PZI and REG COMBINED 85 u.	Fair	None	None	None	Normal
JK	18	6	12	CH—200 gm. P —100 gm. F — 90+	REG and PZI COMBINED 48 u.	Fair	None	None	None	Normal
AH	21	8	13	CH—200 P —100 F — 80	REG and PZI COMBINED 72 u.	Fair	+	None	None	High Normal
AB	21	7	14	CH—250–350 P —100–150 F — 80–115	PZI 48 u.	Poor	++	None	None	Normal
Group II. Diabetes Duration 16–20 Yr.										
SM	26	10	16	CH—180 P — 90 F — 90	REG and PZI COMBINED 30 u.	Good	None	None	None	Normal
JL	25	8	17	Free Diet	PZI 60–70 u.	Poor	+	None	None	Normal
MP	21	3	18	CH—250 P —100 F — 90	REG and PZI COMBINED 32 u.	Fair	None	None	+	Elevated Moderately
MC	25	7	18	CH—200 P —100 F — 70	REG and PZI COMBINED 40 u.	Good	None	None	None	Normal
NC	26	8	18	Free Diet	PZI 60 u.	Very poor	++++	++	++++	Abnormally High
DH	22	3	19	Free Diet	PZI 70 u.	Poor	None	None	None	High Normal
WZ	22	3	19	CH—225 P —100 F —110	REG and PZI COMBINED 60–68 u.	Good	None	None	None	—
Group III. Diabetes Duration 20 Yr. or Longer										
CF	33	13	20	Free Diet	REG and PZI COMBINED 80 u.	Very poor	None	+++	+	Normal
DH	31	11	20	Free Diet	2 inject. Glob. and PZI 90 u.	Very poor	++	+++	++	Slightly Elevated
RG	27	6	21	CH—150 P — 75 F — 90	PZI 75 u.	Good	None	None	None	Normal

TABLE 1—*Continued*

Name	Age (Yr.)	Age (Yr.) at Onset	Duration in Yr.	Average Diet 10 yr.	Insulin	Degree of Control	Complications:			Blood Chemistry: Total Lipids and Cholesterol
							Eye	RG Evidence of Vascular Calcification	Kidney	
HF	27	6	21	CH—250 P —117 F — 96	REG and PZI COMBINED 40 u.	Poor	++	++	++	High Normal
PS	30	9	21	CH—150 P — 75 F — 90	PZI 60 u.	Good	None	None	None	Normal
GZ	32	11	21	CH—200 P — 80 F — 80	REG and PZI COMBINED 42 u.	Fair	None	+	+	Slightly Elevated
IG	48	27	21	CH—200 P — 75 F —100	Separately PZI 15 GLOBIN 8	Good	None	None	None	Slightly Elevated
JS	30	8	22	CH—300 P — 80 F —100	REGULAR 60 u. (twice)	Fair	None	None	None	Slightly Elevated
AW	32	10	22	CH—225 P —125 F —110	REG and PZI COMBINED 65 u.	Fair	None	None	None	Slightly Elevated
JS	38	16	22	Free Diet	PZI 70 u.	Poor	None	++	+	Slightly Elevated
BL	34	11	23	Free Diet	PZI 48 u.	Poor	+	+	+	Normal
YK	30	6	24	CH—180 P — 75 F — 90	2 inject. REG and GLOB 62 u.	Good	None	None	None	Normal
WS	28	3	25	CH—200 P — 90 F —100	REG and PZI COMBINED 54 u.	Poor	+	None	None	Normal
AE	31	3	28	Free Diet	REG and PZI COMBINED 90 u.	Poor	+	None	None	Normal

presence or absence of ketonuria and developmental progress, as indicated by increase in weight, growth, general appearance and sense of well being.

Diabetic retinopathy was present intermittently in all patients after the disease had been present for 3 or more yr. However, most of them had only the typically small hemorrhages with normal retinal vessels. In many of the cases, the punctate hemorrhages disappeared only to reappear at a later time. Recently, with better management and the employment of a diet moderate in calories of carbohydrates and fat and high in protein, there seems to have been fewer recurrences of punctate retinal hemorrhages.

In the column under eye complications, the authors have designated: "One Plus" in those cases who have shown only a persistence or frequent recurrence of the hemorrhagic lesions. All the others whose fundi were normal during the last 2 yr. of the study are excluded. "Two Plus" indicates small hemorrhages and exudate. "Three Plus" signifies the presence of mixed vascular retinopathy. "Four Plus" describes a proliferative retinopathy.

All the cases were examined by competent and qualified staff ophthalmologists. Towards the end

of this study, it was fortunately possible to obtain the cooperation and services of one ophthalmologist who examined all the patients. These examinations were made without his being informed of the patients' "diabetic control."

Roentgenograms of the lower extremities were obtained in all cases and the plus designations indicate the degree of density and extent of calcification of the blood vessels.

Renal involvement is indicated primarily by the presence of albuminuria, and only secondarily by the presence of pathologic elements in the urine, hypertension or abnormal blood chemical findings.

All the patients have had repeated blood studies to determine the levels of total protein, serum albumin and globulin, blood urea nitrogen, nonprotein nitrogen, sugar, total lipids, cholesterol and cholesterol esters, and occasionally phospholipids and other constituents. In the "Blood Chemistry" column in table 1 only total lipids and cholesterol are considered. In the column designated "Kidney," the total protein and its fractions and the blood urea nitrogen are considered.

TABLE 2

DIABETIC PATIENTS WITH COMPLICATION

Diabetes Duration in Yr.	No. of Patients	Vascular Complications of Any Type	Percentage
10–15	4	2	50
16–20	7	3	43
20+	14	8	57
Total	25	13	52

The blood chemical findings did not consistently parallel the clinical findings.

In most of the cases showing evidence of peripheral vascular calcification or of renal complications of diabetes mellitus, elevated total blood lipids and cholesterol were found.

On the other hand examination of the last column of table 1 shows that of 9 patients without complications, 3 showed only slight elevation of the total blood lipids and cholesterol. The rest had normal values. Six other patients whose only complications were 1 or 2+ eye ratings also had normal total blood lipids and cholesterol values.

TABLE 3

INCIDENCE OF COMPLICATIONS IN RELATION TO DURATION OF AND DEGREE OF CONTROL OF DIABETES MELLITUS

Degree of Control Rating	No. of Cases	Cases with Complications	Percentage
Good	7	0	0
Fair	7	3	43
Poor	8	7	88
Very poor	3	3	100

All who showed peripheral vascular calcification had renal complications. Seven cases in the series fall into this category. Of these, 3 had normal blood chemical findings; 4 had elevated blood chemical findings.

One patient in this series (N.C.) died recently. She had had diabetes mellitus for 18 yr. at the time of her death and showed extensive diabetic retinopathy and renal involvement. Death was probably due to congestive heart failure and intercapillary glomerulosclerosis (Kimmelstiel-Wilson disease).

Eight patients had renal complications. Only one of these had no evidence of peripheral vascular calcification. Three had normal total blood lipids and cholesterol, and in 5 there was slight to marked elevation of total blood lipids and cholesterol.

Table 2 concerns itself solely with the relationship between duration of the disease and incidence of diabetic complications. Of the 4 patients who had diabetes mellitus for 11 to 14 yr., 2 demonstrated definite retinopathy but no other complications. The other 2 were free of any demonstrable complications. Of 7 patients who had the disease for 16 to 19 yr., 3 had diabetic complications. One had only diabetic retinopathy, another only renal involvement of a mild degree and the third extensive involvement of eyes, peripheral vessels and kidney.

Of 14 subjects who had diabetes mellitus for 20 or more years, 8 had diabetic complications. Only 2 of the latter displayed retinopathy as the sole complication. The other 6 had both peripheral vascular calcification and renal involvement.

Table 3 is concerned with the relationship between the degree of control of diabetes mellitus and the incidence of diabetic complications. It is clear that none of the patients with good control developed complications. In contrast, those designated as poorly controlled did develop diabetic complications.

TABLE 4

INCIDENCE OF COMPLICATIONS IN RELATION TO DURATION AND SEVERITY OF DIABETES MELLITUS AS INDICATED BY INSULIN REQUIREMENTS

Insulin Requirements in Units	No. of Cases	Cases with Complications	Percentage
20–40	3	2	67
40–60	9	4	44
60–80	10	5	50
over 80	3	1	33

In table 4 an attempt is made to determine whether the insulin requirement bears any relationship to the incidence of complications. No such definite relationship could be demonstrated. There were many patients who received large doses of insulin and developed no complications. It is rather the duration and the degree of control of the diabetes mellitus that stand out as 2 positive factors in the incidence of diabetic complications.

DISCUSSION AND SUMMARY

In diabetes mellitus we are dealing primarily with a profound carbohydrate disturbance in which a state of hypoinsulinism plus imbalance of the anterior pituitary and adrenal cortical hormones are present. This extensive disturbance affects metabolic functions of many organs and tissues. Because of the interrelationship between carbohydrate, protein and fat and even mineral and water metabolism, there must be varying degrees of change both normal and abnormal, in all of these metabolic processes. The aberrations may be transitory or more prolonged, depending upon the persistence and severity of the metabolic derangement. Since no juvenile diabetic patient, even with the assistance of present-day insulin and prescribed diet, can respond in a completely physiologic manner to his food intake, activity, etc., we must expect metabolic deviations from the normal. It is logical to assume that the closer the approximation of the diabetic patient to a normal physiologic state, the more desirable it is and the less likely is he to suffer qualitatively and quantitatively from the results of his metabolic disorder.

In this small series to date none of the patients whose control was considered good developed detectable vascular lesions even though they had the disease for 10 to 28 years.

This survey adds to the slowly accumulating clinical data indicating decided benefits of a well controlled diabetic state in humans.[2–6]

ACKNOWLEDGMENT

The authors wish to express their gratitude and indebtedness to Dr. Bernard Epstein for the roentgenographic studies; to Dr. Joseph Mandelbaum for the ophthalmoscopic examinations; to Dr. Albert Sobel for the blood chemical studies; to Dr. Anna Wagner for the electrocardiographic studies; and to Drs. Benjamin Kramer and Leo S. Radwin for their generous help in the editing of the paper.

REFERENCES

1. Collens, W., and Grayzel, H. G., Management of ambulatory diabetic child, Am. J. Dis. Child. **38**:275, 1929.
2. Jackson, R. L., and others, Degenerative changes in diabetic patients and level of control, PEDIATRICS **5**:959, 1950.
3. Watson, B. A., Prevention of diabetes, J. Clin. Endocrinol. **2**:414, 1942.
4. Lukens, F. D. W., Incentives to treatment of diabetes mellitus, M. Clin. North America **31**:387, 1947.
5. Watson, B. A., Arrest in development of diabetes, Proc. Am. Diabetes A. **9**:331, 1949.
6. Doeschner, C. W., Deisher, R. W., and Hartmann, A. F., Later status of juvenile diabetes, J. Pediat. **38**:8, 1951.

SPANISH ABSTRACT

"Survey" Clinico de las Complicaciones Vasculares de la "Diabetes Mellitus Juvenil"

Un estudio de 25 casos de "diabetes juvenil" que han tenido su enfermedad durante 11 a 28 años reveló que hasta el momento presente ninguno de los pacientes considerados bien controlados desarrollaron lesiones vasculares apreciables. No hay duda que la incidencia de complicaciones diabeticas aumentan con la duración de la enfermedad. Sin embargo se estima que un buen control posiblemente retarda el comienzo de las complicaciones diabeticas en un número apreciables de casos y en una forma similar influye sobre la severidad de estas complicaciones.

555 Prospect Place

STUDIES ON PREMATURITY

IV. Influence of Fetal Maturity on Weight Lag Period

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DURING the course of an investigation of factors influencing mortality of premature infants born at the Jewish Hospital of Brooklyn, it was noticed that the initial lag in weight gain of the infants varied greatly. The variation appeared to be unrelated to the birth weight of the infant. Thus, the period required for recovery from initial weight loss and for continued progress beyond birth weight was in many instances more than twice as long as that in other infants of comparable birth weight. It was therefore impossible to predict at the time of birth how long it would be necessary for a given infant to be hospitalized. Since previous studies[1] indicated that gestational maturity of the premature infant was an important factor in its survival, it was thought that the same factor might perhaps account for the variability noted with respect to initial gains of weight. Accordingly, the present study was undertaken to determine the relationship of maturity and of birth weight to initial loss and gain of weight of the premature infant.

Analysis was made of the data pertaining to the group of premature infants born at the Jewish Hospital of Brooklyn during the five year period between 1941 and 1945. For reasons discussed in an earlier report,[2] only those infants weighing less than 2250 gm. were included. Again, as in previous reports, the infants were divided into three weight classes and four gestation periods. Infants weighing less than 1000 gm. were not considered since there was but one survival in this group. The time required for each infant not only to regain its birth weight but also to continue to increase in weight was determined. This period has been designated as the weight lag period in the analyses which follow.

The present study was made on 635 surviving infants. One was excluded because it weighed less than 1000 gm. Eleven infants were excluded because of intercurrent infections or because their weight lag periods could not be determined definitely.

The infants were placed on a standardized fluid and feeding regimen following a preliminary starvation period of from 24 to 72 hours depending on birth weight and clinical condition. The initial feedings consisted of 5% dextrose solution totalling 32 cc. for the first 24 hours. The dextrose solution was then replaced with increasing proportions of a standard evaporated milk formula with 5% added carbohydrate. The fluid and caloric intake were gradually increased so that within about two weeks the infants were receiving 150 cc. of fluid and 125 cal./kg./day. A supplementary aqueous polyvitamin preparation (vifort® 0.6 cc. daily) was incorporated in the diet on the fifth day of life.

In table 1 are given the median weight lag periods for each weight group and gestation period. From the horizontal columns it will be seen that the lag period for each weight group varied in an inverse relationship with the length of the gestation period. Thus, for babies weighing between 1000 and 1499 gm. the median weight lag periods varied

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from 16 to 5 days in a pattern indicating that the more mature the infant, the shorter was the lag period. The same relationship held for the other two weight groups. On the other hand, the lag period for infants in each of the gestation groups was almost the same regardless of the birth weight. The independence of the lag period and the birth weight is readily apparent when one reads the figures for lag period vertically in table 1.

The results were subjected to statistical analysis by the Chi square method. In table 2 are given calculations testing the assumption that the median weight lag period is depend-

TABLE 1

WEIGHT LAG PERIOD* IN RELATION TO MATURITY (GESTATION PERIOD) AND BIRTH WEIGHT

Wt.	Gestation Period (wk.)				Total
	26–29	30–33	34–37	38–40	
I. 1000–1499 gm.					
No. of cases	11	22	12	4	49
Range of wt. lag period (days)	4 to 35	1 to 33	3 to 13	4 to 6	1 to 35
Median wt. lag period (days)	16	11	5	5	8
II. 1500–1999 gm.					
No. of cases	4	95	103	45	247
Range of wt. lag period (days)	2 to 19	4 to 24	3 to 25	3 to 13	2 to 25
Median wt. lag period (days)	9	11	7	4	7
III. 2000–2250 gm.					
No. of cases		33	172	122	327
Range of wt. lag period (days)		2 to 24	2 to 19	1 to 17	1 to 24
Median wt. lag period (days)		12	6	4	5
Total					
No. of cases	15	150	287	171	623
Range of wt. lag period (days)	2 to 35	1 to 35	2 to 25	1 to 17	
Median wt. lag period (days)	13	11	6	5	

* Lag period represents time in days necessary for infant to regain birth weight and continue to gain.

ent principally on birth weight. Here the value of $X^2 = 51.4$, which for 11 degrees of freedom makes P much less than 0.01.[3] The assumption that the median weight lag period depends principally on the birth weight is therefore not justifiable.

Similarly, in table 3 are given calculations testing the hypothesis that the median weight lag period is determined principally by the maturity of the infant. In this case $X^2 = 10.2$, which for 11 degrees of freedom makes P almost equal to 0.5,[3] a result which favors the hypothesis.

A comparison of the weight lag periods of twins showed, in most cases, little variation in spite of marked differences in the birth weights of these siblings. Since the duration of gestation of twin siblings is the same, it lends further support to the thesis that there is greater dependence of weight lag period on the maturity of the infant than on its birth weight.

In brief, these results indicate that median weight lag period is determined principally by the period of gestation and is little, if at all, affected by the weight of the infant. It

should be emphasized that in each group there are variations in the weight lag period, indicating that in the individual case other factors may also play a role.

That maturity of the infant has considerable importance has been indicated by the data published in previous reports. Thus, in a study of fatality rates,[1] it was found that premature infants born after longer gestation periods had lower mortality rates than those born after shorter gestation periods. A later report[4] demonstrated the significance of maturity in the analysis of premature infant fatality rates among babies born of mothers

TABLE 2

CHI SQUARE TEST FOR SIGNIFICANCE OF RELATIONSHIP BETWEEN BIRTH WEIGHT AND MEDIAN WEIGHT LAG PERIOD

Wt.	Gestation Period (wk.)				Median Wt. Lag Period, Days
	26–29	30–33	34–37	38–40	
1000–1499 gm.					
No. of cases	11	22	12	4	
Expected*	5½	11	6	2	8
Observed	2	7	10	4	
X^2	2.3	1.5	2.7	2.0	
1500–1999 gm.					
No. of cases	4	95	103	45	
Expected†	2	47½	51½	22½	7
Observed	2	18	46½	33½	
X^2	0.0	18.1	0.5	5.4	
2000–2250 gm.					
No. of cases		33	172	122	
Expected‡		16½	86	61	5
Observed		6	57	73	
X^2		6.7	9.8	2.4	

$\Sigma X^2 = 51.4$

n (D.F.) = 11

P = <0.01 [For 11 degrees of freedom and $X^2 = 24$, P = 0.01]

* No. of cases expected with median wt. lag less than 8 days.

† No. of cases expected with median wt. lag less than 7 days.

‡ No. of cases expected with median wt. lag less than 5 days.

who had toxemia of pregnancy. Here it was found that the over-all fatality rate for premature infants born of mothers with toxemia of pregnancy was actually lower than that in the case of infants born of nontoxemic mothers. When the fatality rates were analyzed in relationship to the maturity of the infants, it was found that the lower fatality rate for the infants born of mothers with toxemia of pregnancy could be explained by the greater gestational age of these babies. Similarly, the lower over-all fatality rate of premature twins[1] was found to be due to their greater maturity at birth. These observations, then, serve to point up the importance of gestation period (maturity) as a factor influencing the fate of premature infants. It is interesting that a similar point of view is implicit in a recent report of the Expert Committee on Health Statistics in connection with the standardization of statistics of live births and fetal deaths.[5]

TABLE 3

CHI SQUARE TEST FOR SIGNIFICANCE OF RELATIONSHIP BETWEEN MATURITY (GESTATIONAL PERIOD) AND MEDIAN WEIGHT LAG

	Gestation Period (wk.)			
	26–29	30–33	34–37	38–40
1000–1499 gm.				
No. of cases	11	22	12	4
Expected	5½*	11†	6‡	2§
Observed	4½	11½	8½	2
X^2	0.2	0.0	1.0	0.0
1500–1999 gm.				
No. of cases	4	95	103	45
Expected	2*	47½†	51½‡	22½§
Observed	3	39½	40½	24½
X^2	0.5	1.3	2.3	0.2
2000–2250 gm.				
No. of cases		33	172	122
Expected		16½†	86‡	61§
Observed		12½	75½	73
X^2		1.0	1.3	2.4
Median lag (days)	13	11	6	5

$\Sigma X^2 = 10.2$
n (D.F.) = 11
P = 0.50 nearly

* No. of cases expected with median wt. lag less than 13 days.
† No. of cases expected with median wt. lag less than 11 days.
‡ No. of cases expected with median wt. lag less than 6 days.
§ No. of cases expected with median wt. lag less than 5 days.

SUMMARY AND CONCLUSIONS

The weight lag periods of 623 premature infants with birth weights ranging between 1000 and 2250 gm. were studied. It was found that the time required for a premature infant to regain its birth weight and continue to gain (weight lag period) was inversely related to the length of its gestation period.

The importance of considering gestation period (degree of maturity) in studies of premature infants is emphasized.

REFERENCES

1. Steiner, M., and Pomerance, W., Studies on prematurity. II. Influence of fetal maturity on fatality rate, PEDIATRICS 6:872, 1951.
2. Pomerance, W., and Steiner, M., Studies on prematurity. I. Incidence and obstetrical considerations, Am. J. Obst. & Gynec. 60:333, 1950.
3. Fischer, R. A., Statistical Methods for Research Workers, London, Olive & Boyd, Ltd., 1930.
4. Pomerance, W., and Steiner, M., Studies on prematurity. III. Influence of toxemia of pregnancy on fatality rate, Am. J. Obst. & Gynec., to be published.
5. International Recommendations on Definitions of Live Birth and Fetal Death, Publication 39, Federal Security Agency, USPHS, National Office of Vital Statistics, 1950.

SPANISH ABSTRACT

Estudios del Prematuro. IV. Influencia de la Madurez Fetal sobre el Periodo de Perdida de Peso Inicial

Durante el curso de una investigación de los factores influyentes sobre la mortalidad de los prematuros, se notó que la perdida de peso inicial de los niños varió grandemente y no estuvo relacionada con el peso al nacer. El presente estudio se realizó con el proposito de determinar la relación entre la madurez fetal y peso al nacer, con la perdida ó ganancia de peso de los prematuros en el periodo de perdida de peso inicial. Se estudió el periodo de perdida de peso de 623 prematuros cuyos pesos al nacimiento oscilaron entre 1000 y 2250 gramos. Se encontró que el tiempo requerido por un prematuro para volver a alcanzar su peso al nacer y continuar aumentando estaba inversamente relacionado con la extensión del periodo de gestación.

Los autores señalan la importancia de considerar el periodo de gestación (madurez fetal) en los estudios sobre los prematuros.

555 *Prospect Place*

METHOD OF OBTAINING ANAEROBIC ARTERIAL BLOOD SAMPLES FROM INFANTS

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Boston

A SATISFACTORY method for obtaining anaerobic arterial blood samples from newborn infants requires at least the following conditions:

1. It must be safe.
2. The sampling must be sufficiently rapid to give blood values for any given half a minute or less.
3. Pain must be minimal so that crying can be avoided.
4. Repeated sampling on one infant should be possible.

Arterial puncture is both safe and rapid in only a few experienced hands and repeated sampling is even less safe or sure. Crying is seldom avoided.

Cutaneous bleeding from heel puncture frequently produces mixed blood and bleeding is almost always too slow to give an accurate picture of the state of the blood at a given moment. Crying is the rule. In addition, the usual method of collection under oil introduces further inaccuracies: oil slows the bleeding, absorbs a considerable amount of carbon dioxide, and is extremely difficult to exclude from pipettes.

The present investigators have evolved a method which has proved satisfactory in about 50 consecutive cases. "Cutaneous" arterial blood is sampled from the foot, the site of puncture being over the soft tissue area containing the plexus of arterioles from the lateral malleolar artery (Fig. 1).

EQUIPMENT

Three pieces of equipment, easily made in any laboratory, are required:

1. As shown in Fig. 2, this consists of a 1″ × 1″ square of adhesive tape which has a centrally punched hole of ⅛″ diameter, centered over which and sealed by rubber cement is a ¼″ length of soft rubber tubing of ⅛″ bore and 3/32″ wall thickness.
2. As shown in cross section (Fig. 3), a glass transferring tube composed of a ¾″ tapered capillary of 1/16″ inner diameter over the base of which is cemented a ⅜″ length of glass tube of ¼″ outer diameter. The tip is ground to fit the tips of blood pipettes.
3. A scalpel of about ⅛″ width.

METHOD

The foot should be warm. To insure full vasodilatation and rapid blood flow from the incision it is wise to keep hot compresses on the foot to be used, for 5 min. It is then cleaned with soap and warm water, dried, and the square of adhesive firmly and smoothly applied so that the center hole is situated above the spot where the puncture is to be made.

When a sample is required, a cruciform incision, ⅛″ in depth, is made with the scalpel blade, through the hole in the rubber (Fig. 4a). A drop of blood wells up into the rubber tubing and the

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glass transferring tube is pushed in quickly, almost, but not quite, as far as the skin (Fig. 4b). It fills immediately with blood and flows over. The initial drop, already exposed to air, is wasted. Then the tip of a blood pipette can be approximated to the tip of the transferring tube and filled (Fig. 4c).

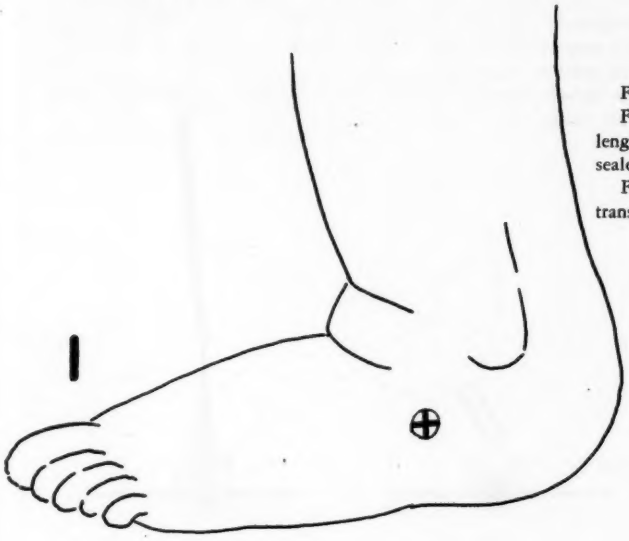
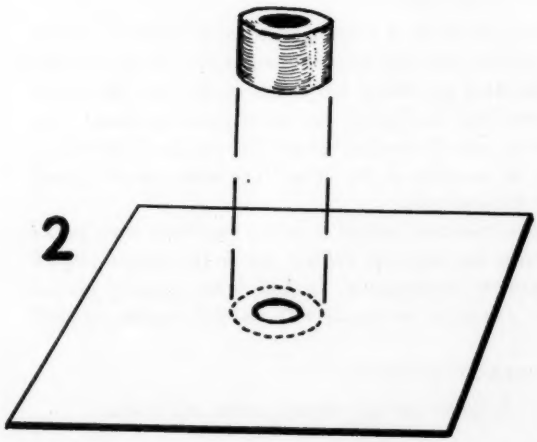
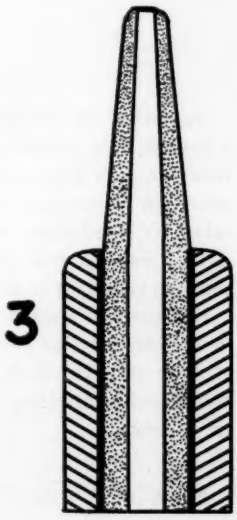


FIG. 1. Site of puncture.

FIG. 2. Square of adhesive and length of rubber tubing to be sealed upon it.

FIG. 3. Cross section of glass transferring tube.





In an average case, there is enough rapidly flowing blood to fill two 40 cmm. pipettes (micro Scholander-Roughton) and one pipette of 100 cmm. capacity (Shock-Hastings).

Bleeding can be controlled readily after the adhesive and glass transferring tube are removed and in the authors cases the incisions have all healed rapidly.

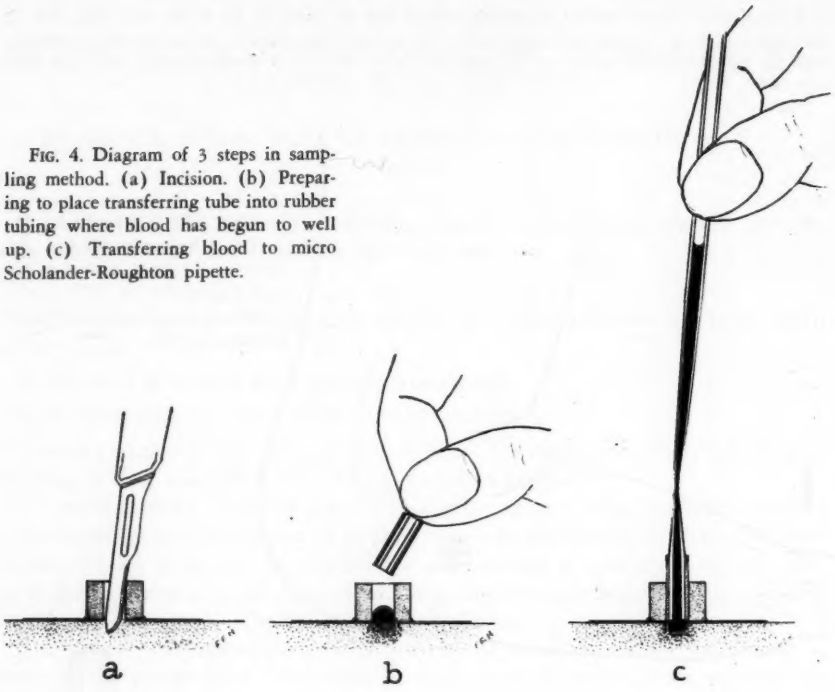


FIG. 4. Diagram of 3 steps in sampling method. (a) Incision. (b) Preparing to place transferring tube into rubber tubing where blood has begun to well up. (c) Transferring blood to micro Scholander-Roughton pipette.

DISCUSSION

Because of the hazardous procedure involved in arterial puncture in newborn infants, it has not been possible to make comparisons with arterial blood drawn simultaneously. However, such work as that of Lilienthal and Riley[1] has demonstrated that the oxygen saturation of cutaneous blood drawn from the heated ear shows good agreement with values for blood drawn simultaneously from the brachial artery; and the blood the present authors obtained from this plexus of arterioles in the infant foot flows rapidly uphill, although capillarity is almost nil at the bore used.

Hultgren and Hackett,[2] who used a collection method requiring the blood drops to fall through air for 1 or 2 cm., found that this exposure did not change the oxygen content of their samples. Since, in the present investigators' method, with properly ground pipette and transferring tube, there should be no contact with air, the samples obtained are anaerobic.

ACKNOWLEDGMENT

Appreciation is due Dr. Clement A. Smith for his encouragement and advice.

REFERENCES

1. Lilienthal, J. L., Jr., and Riley, R. L., On determination of arterial oxygen saturations from samples of "capillary" blood, J. Clin. Investigation **23**:904, 1944.
2. Hultgren, H. N., and Hackett, Adeline J., Determination of oxygen content of capillary blood in congenital heart disease, PEDIATRICS **6**:93, 1950.

SPANISH ABSTRACT

Método para la Obtención de Muestras de Sangre Arterial Anaeróbica de Niños

Con el objeto de obtener repetidas muestras de sangre arterial anaeróbica de niños recién nacidos, de una manera rapida, segura, y con dolor minimo de modo que el llanto pueda evitarse, el siguiente método cutáneo para la extracción de muestras de sangre fué desarrollado. Por medio de un tubo especial de cristal aplicado directamente sobre una incisión en forma de cruz, hecha sobre el tejido blando que contiene los plexos arteriolares de la arteria maleolar lateral, la sangre es transferida directamente a las pipetas usadas para el análisis de oxigeno y anhidrido carbonico.

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FIBROUS STERNOMASTOID TUMOR OF INFANCY

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New York City

THE fibrous sternomastoid tumor of infancy, often associated with muscular torticollis, has been given scant attention by pediatric authors. Recent reports on these tumors are found almost exclusively in orthopedic and surgical journals, with little participation by pediatricians. This report deals with a typical case and review of current concepts concerning this entity.

REPORT OF CASE

P.R. was born to a healthy 28 yr. old primipara. Pregnancy, labor and delivery were uneventful. The infant was a vigorous male, weighing 3.6 kg. at birth. He took breast feedings well and weighed 4.8 kg. at 9 wk. of age, when the family pediatrician first detected a mass in the neck which was firm, smooth and ovoid, measured 3 x 1 cm. and was inseparable from the insertion of the left sternomastoid muscle. With the head rotated to the right, the swelling became visible on the left. It was not fixed to the skin and was movable only in a horizontal plane with the muscle. The head was not tilted to either side and there was no apparent limitation of active or passive motion. The remainder of the physical and laboratory examination was not contributory. Roentgenograms of the chest and neck were normal.

A diagnosis of fibroma or fibrosarcoma was made and excision advised. Operation was performed at 2 mo. of age. The left sternomastoid muscle was exposed by a low transverse cervical incision. The lower portion of the muscle was replaced by a dense, glistening, gray mass which extended cephalad for about 5 cm. from the clavicular insertion, merging with the normal muscle in an irregular infiltrating fashion. The bulk of the sternomastoid muscle was resected, with care to avoid injury to the spinal accessory nerve. The wound healed by primary union. A plaster cast was not applied. The mother manipulated the head in all directions daily for a month. When the patient was last seen 8 mo. postoperatively, there was a full range of motion of the head in all directions.

Pathology report: The specimen was a solid tubular structure measuring $3\frac{1}{2} \times 1\frac{1}{2} \times 1\frac{1}{2}$ cm. in greatest diameters. The external surface was covered by tags of deep red-brown, obvious muscle everywhere except where glistening gray tissue appeared on the cut surface. Sections revealed the interior to consist of lobulated, glistening pale gray, firm tissue which merged imperceptibly with the adjacent muscle.

Microscopic description: Sections were stained with hematoxylin-eosin, Van Gieson and Masson stains. At the periphery of some sections, essentially normal striated muscle fibers were noted. For the most part, however, isolated widely separated muscle fibers were enmeshed in mats of cellular fibrous tissue. In many fields, areas of muscle were replaced by cellular fibrous connective tissue. Most of the fibroblasts were loosely packed, plump, spindle-shaped cells within the nuclei of which only a very rare mitotic figure was noted. Within the isolated enmeshed muscle fibers, changes such as variation in staining characteristics, swelling, vacuolization, loss of striation and multinucleation were seen. There was no evidence of old or recent hemorrhage. All the vessels were patent (Fig. 1 and 2).

The pathologic diagnosis was fibrous sternomastoid tumor.

DISCUSSION

1.. The natural history of these tumors has been studied in 90 cases by Middleton,[1] in 117 cases by Hulbert[2] and in 225 cases by Chandler.[3,4] The mass is usually first detected

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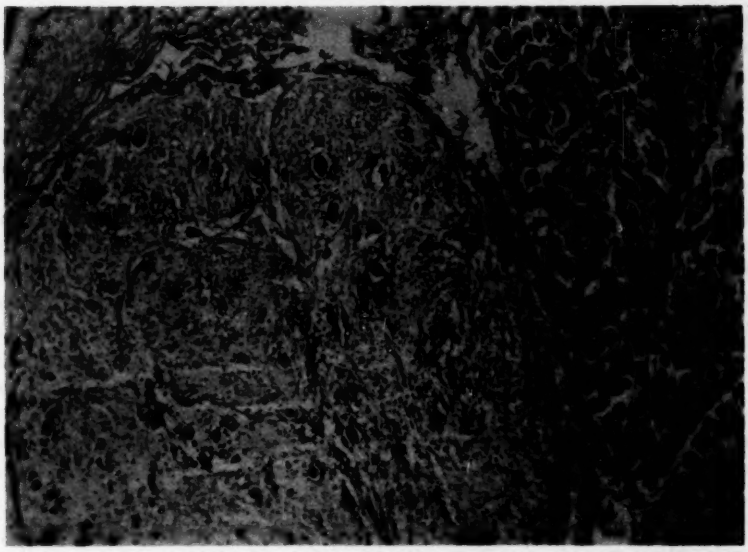

FIG. 1. Section demonstrating peripheral rim of normal muscle and area consisting largely of cellular fibrous connective tissue within which isolated muscle fibers are enmeshed. (Original 105 ×.)

FIG. 2. Section illustrating abnormalities of muscle fibers noted in text and adjacent fibroplastic zone. (Original 105 ×.)

after 10 days of age as a fusiform swelling in one sternomastoid muscle. Bilateral involvement has been reported in several instances.[5] Often the swelling increases in size for 2 to 4 weeks, remains stationary for 2 to 3 months, and then gradually regresses. It usually disappears completely in 4 to 8 months. The tumor is firm and often cartilaginous in consistency. It is not cystic or fluctuant and does not clinically resemble a hematoma. When the tumor disappears, the muscle feels short and fibrous. Usually the tissue at the site is converted into a firm fibrous scar histologically. When the tumor is at its height, a transient torticollis may be noted. In some cases a true torticollis develops when the tumor begins to regress in size. After the mass has regressed, limitation of motion of the head can sometimes be detected on clinical examination, although wry neck distortion or associated skeletal deformities are not present. Persistent torticollis is not usually noted until the third or fourth year of life, when the short neck of the infant lengthens into that of the young child. Occasionally, torticollis, associated with skeletal deformities, clavicular or mastoid exostoses, or facial asymmetry are not detected until years after the mass has regressed and been forgotten. In approximately one-fifth of the cases of congenital muscular torticollis a history of antecedent sternomastoid tumor is obtained. The tumor usually regresses spontaneously and there is no residual deformity in four-fifths of the cases.

2. Pathogenesis: The pathogenesis of the fibrous sternomastoid tumor of infancy is unknown. Many theories of etiology have been proposed. Stromeyer's[6] concept that the basic lesion is a hematoma of the muscle due to birth trauma is no longer tenable. Middleton suggested, on the basis of experimental observations, that the tumor, and therefore muscular torticollis, resulted from a temporary acute venous obstruction in the muscle which occurred during labor. His survey of the birth histories of his cases for situations conducive to venous obstruction disclosed a significant proportion in which labor was complicated or prolonged. Chandler and Altenberg[4] reported a still higher incidence of abnormal deliveries. They suggested that a pre-existing uterine torticollis prevented normal engagement of the fetal head, and concluded that an unexplained change in the muscle prior to birth, intra-uterine malposition, and probable trauma at birth were additional etiologic factors. A satisfactory explanation is still not available for the etiology of these tumors.

3. Differentiation from Malignant Neoplasm: The occurrence of a sternomastoid mass, unassociated with torticollis, presents the clinician with the problem of the differential diagnosis of the fibrous sternomastoid tumor of infancy from neoplastic masses. Farber offered the dictum: "Every solid mass in an infant or child should be regarded as a malignant tumor until its exact nature is determined by histologic examination of the removed tumor."[7] There does not seem to be a recorded case of malignancy of the sternomastoid muscle in a young child except for the case of fibrosarcoma described by Milch in 1945.[8] This child was eventually referred to the Montefiore Hospital, where she has been followed to date. The characteristic clinical history of this case and the present well being of the child support the present authors' interpretation of the original slides as a fibrous sternomastoid tumor of infancy rather than a fibrosarcoma. The tumor registry of the American Academy of Pediatrics has no record of a single authenticated case of fibrosarcoma of the sternomastoid in infancy, and there are none in the files of the Children's Medical Center in Boston.[9-11] The differential diagnosis between benign and malignant muscle tumors depends upon microscopic evaluation. However, the procedure of biopsy or excision of all such muscle masses to rule out sarcoma would seem

unwarranted, in view of the failure to find an unequivocal instance of malignancy at this site in infants.

4. Treatment: It has been a traditional practice to treat such tumors by conservative measures such as manipulation, and to resort to surgery only when torticollis occurs. Pediatricians who observe masses regress without sequelae are prone to adopt an attitude of watchful waiting. By contrast, orthopedists and reconstructive surgeons who are presented with the complications of these tumors, such as torticollis, skeletal deformities and facial asymmetry favor early surgery. A trend toward early resection was initiated by Chandler and Altenberg in 1944.[4]

Chandler[3] advocated early excision in very young infants on the basis of uniformly good results and the prevention of more fixed skeletal deformities. Speed[12] was among those favoring early resection.[11] Subsequent reports on early prophylactic surgical correction have appeared by Brown and McDowell,[13] Brown, McDowell and Fryer[14] and by Larson and Rosenow.[15] The latter advocate removal of the diseased muscle whenever a definite tumor is present. On the other hand the pediatric surgeon, Wyatt, discussing their paper, suggested that the optimum time for surgery was when the tumor "feels like a cartilaginous mass about the size of an olive." Many surgeons do not agree on the advantage or the necessity of early excision. Key[16] advises against operating on such children until they are at least 2 years of age. Hulbert[2] contends that excision of the tumor in infancy is unjustifiable since four-fifths of all cases of sternomastoid tumors resolve spontaneously without deformity. The present authors believe early management should be conservative, with reservation of surgery for the sequelae of the tumor. Passive neck exercises, consisting of hyperextension of the involved sternocleidomastoid muscle, instituted when the mass is first noted and continued for several months after regression has occurred, may be of value in overcoming the muscle shortening responsible for the subsequent torticollis reported in about 20% of cases.

It is a curious paradox that this highly controversial subject, concerning which there is so little unanimity of opinion, has evoked no recent significant contribution on the part of pediatricians, who occupy the most advantageous position from which to evaluate these lesions.

Summary and Conclusions

A case of sternomastoid tumor of infancy is described which presented clinically as a neck mass without torticollis and simulated a neoplasm.

Four aspects of the problem are discussed: (1) the relationship of tumor and torticollis; (2) the etiology and pathogenesis; (3) the differential diagnosis from sarcoma; and (4) the treatment.

Prophylactic resection of the mass to exclude a possible malignant tumor or to prevent the subsequent development of torticollis, is not justified, since in about 80% of cases spontaneous regression occurs without sequelae.

The institution of passive neck exercises over a period of several months during and following degression of the mass may contribute to a decreased incidence of deformities.

References

1. Middleton, D. S., Pathology of congenital muscular torticollis, Brit. J. Surg. **18**:188, 1930.
2. Hulbert, K. F., Congenital torticollis, J. Bone & Joint Surg. **32**:50, 1950.
3. Chandler, A., Muscular torticollis, J. Bone & Joint. Surg. **30**:566, 1948.
4. Chandler, A., and Altenberg, A., Congenital muscular torticollis, J. A. M. A. **125**:476, 1944.

5. Von Muralt, R. H., Bilateral occurrence of congenital muscular torticollis, Helvet. pediat. acta **1**:349, 1946.
6. Stromeyer, L., Beitrage zur operatioen orthopaedin, oder erfahrungen ueber die subcutane durchschneidung verkurzter muskein und deren sennen, Hanover, Helwing, 1838.
7. Farber, S., in Mitchell-Nelson Textbook of Pediatrics, ed. 5, edited by W. E. Nelson, Philadelphia, Williams & Wilkins Company, 1950, p. 1490.
8. Milch, H., Torticollis due to sarcoma of sternomastoid muscle, Bull. Hosp. Joint Dis. **6**:61, 1945.
9. Dargeon, H., Personal communication to the authors.
10. Farber, S., Personal communication to the authors.
11. Wells, H. G., Occurrence and significance of congenital malignant neoplasms, Arch. Path. **30**: 535 and 597, 1940.
12. Speed, J. S., in discussion of Chandler,[3] p. 588.
13. Brown, J. B., and McDowell, F., Wry neck facial distortion prevented by resection of fibrosed sternomastoid muscle in infancy and childhood, Ann. Surg. **131**:721, 1950.
14. Brown, J. B., McDowell, F., and Fryer, M. P., Facial distortion in wry neck prevented by early resection of fibrosed sternomastoid muscle, Plast. & Reconstruct. Surg. **5**:301, 1950.
15. Larson, L. M., and Rosenow, J. H., Fibrous sternomastoid tumors of infancy: Role in etiology of muscular torticollis, Minnesota Med. **31**:1243, 1948.
16. Key, J., in discussion of Chandler,[3] p. 588.

SPANISH ABSTRACT

Tumor Fibroso del Esterno-cleido-mastoideo en la Infancia

Se presenta un caso tipico de tumor fibroso benigno del esterno-cleido-mastoideo de la infancia, el cual se presentó clinicamente sin torticolis y semejando una neoplasia. Los autores revisan la historia natural de estos tumores, señalandose la relación entre los torticolis musculares congénitos y la tendencia a la regresión espontanea sin deformidad residual en 4/5 de los casos. No existe una explicación satisfactoria de la etiología de estos tumores. Tampoco se han reportado casos inequivocos de malignidad en este sitio en niños. Se discute la tendencia reciente hacia la extirpación temprana de estos tumores, pero se recomienda la practica tradicional de un tratamiento conservador, reservando la cirugía para las sequelas del tumor.

Gun Hill Road, near Jerome Avenue

PRODUCTION OF CONGENITAL DEFECTS IN THE OFFSPRING OF PREGNANT MICE TREATED WITH CORTISONE

Progress Report

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ONE of the major gaps in medical knowledge today concerns the causes of congenital defects. Interest in this problem has been stimulated by the discovery, in recent years, that a number of environmental agents, when applied to pregnant animals, will cause congenital defects in the offspring. These agents include dietary deficiencies in vitamin A,[1-11] riboflavin,[12-15] pantothenic acid [16,17] and folic acid;[18,19] x-radiation;[20-33] hypoxia;[24] injection of trypan blue,[25] nitrogen mustard[26] and possibly desoxycorticosterone acetate.[27] In general, the incidence and type of defect vary according to the agent used, its dosage, the stage of gestation at which it is applied and the genetic constitution of the animal involved.

Recently, cortisone has been added to the list of agents which will cause intrauterine developmental disturbance in the embryo when applied to the pregnant mother.[28,29] The present paper reports the data which have accumulated to date during the authors' studies on this interesting phenomenon.

EXPERIMENTAL WORK

Materials and Methods: The mice used in the experiments to be described below were raised in the mouse colony of the Department of Genetics, McGill University, on a diet of Purina Fox Chow and water *ad libitum*, supplemented twice a week with bread, milk and lettuce. Five genetically different groups of mice were used. Three of these were stocks originally received from the Jackson Laboratory at Bar Harbor and have been inbred by brother-sister matings for many generations. They were (1) strain A, (2) C57 Black and (3) Black and tan. The other 2 groups were (4) a stock carrying the mutant "Naked" and inbred in this laboratory for 11 generations of brother-sister matings and (5) a genetically heterogeneous stock derived from the F_2 and F_3 generations of a cross between 2 other strains. The 5 groups will hereafter be referred to as A, C57, B, N and H, respectively. No cases of cleft palate without harelip have been observed in any of 59 offspring of untreated mice of these strains examined specifically for this defect.

One male and 3 or 4 females of the same strain were kept in each cage and the females were checked regularly for the presence of vaginal plugs or palpable embryos. If a vaginal plug was found or pregnancy was diagnosed by palpation, the female was isolated in a separate cage until at least 2 days after parturition. In those animals in which a vaginal plug was seen, the stage of gestation at which the injections were given was accurately known.[30] For the others, gestational stage could be estimated by palpation and by counting back from the day of parturition, assuming an average gestational period of 19 days. Estimates derived by these 3 methods corresponded very well. Isolated females were weighed and examined daily, and were checked more frequently from the 18th day on, so that the newborn mice could be examined as soon as possible after birth.

The cortisone used in these experiments was the Merck Cortone® preparation, a saline suspen-

From the Department of Genetics, McGill University, and the Children's Memorial Hospital of Montreal.

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TABLE 1

INCIDENCE OF CLEFT PALATE IN OFFSPRING OF PREGNANT MICE GIVEN 4 DAILY DOSES OF CORTISONE

Strain	Daily Dose (mg.)	Day of Gestation Treatment Started	No. of ♀♀ Treated	Total Young	No. with Cleft Palate
A	10.00	12	1	litter	resorbed
	5.00	9	1	litter	resorbed
	2.50	8	2	litters	resorbed
	2.50	9	1	2	1
	2.50	10	3	7	7
	2.50*	12	3	17	8
	2.50	13	1	1	0
	2.50	14	4	14	6
	2.50	16	1	4	1
	1.25	11	1	6	4
	1.25	12	1	7	0
	0.625	10	1	4	0
	0.625	12	1	8	0
N	2.50	10	3	7	7
	2.50	11	1	5	5
	2.50*	12	1	5	2
	2.50	13	1	4	2
	2.50*	14	1	6	0
	1.25	6	1	2	2
	1.25*	10	2	10	4
	1.25	11	1	8	7
	1.25*	13	2	10	1
	0.625	10	1	2	0
	0.625	11	1	8	0
	0.625	12	1	9	0
	0.625	13	1	6	0
C57	5.00†	11	2	1	1
	2.50	8	1	3	2
	2.50	9	3	7	3
	2.50	10	5	10	4
	2.50	11	4	11	1
	2.50	12	7	38	4
	2.50	13	2	9	0
	2.50	14	2	8	0
	1.25	11	1	8	0
	1.25	14	1	6	0
B	5.00	11	1	3	0
	2.50	8	1	litter	resorbed
	2.50	9	1	4	2
	2.50	10	2	8	4
	2.50	12	4	34	1
	2.50	13	2	9	0
	2.50	15	1	8	0
	0.625	12	1	8	0
H	5.00	11	1	3	0
	2.50	9	1	3	1
	2.50	11	2	9	5
	2.50	12	3	21	4
	2.50	14	2	12	1
	1.25*	11	2	19	0

* 1 litter given 5 daily doses.

† 1 litter aborted.

TABLE 2

INCIDENCE OF CLEFT PALATE IN OFFSPRING OF PREGNANT MICE GIVEN 4 DAILY DOSES OF CORTISONE 2.5 OR 1.25 MG.

Day of Gestation Treatment Started	Strains A and N				Strains C57, B and H			
	No. of ♀♀ Treated	Total Young	No. With Cleft Palate	% With Cleft Palate	No. of ♀♀ Treated	Total Young	No. With Cleft Palate	% With Cleft Palate
<10	4++	4	3	—	7+	17	8	47.1
10–11	11*	43	34	79.1	16*	65	14	21.5
12–13	9***	44	13	29.5	18	111	9	8.1
14–17	6	24	7	29.2	6	34	1	2.9

Each + represents one litter which was resorbed.
Each * represents one female given 5 daily doses.

sion containing cortisone acetate 25 mg./cc. with added suspending agents and 1.5% benzyl alcohol. It was given intramuscularly, in the flank. Doses of 10, 5, 2.5, 1.25 and 0.625 mg./day were used and (with the exceptions noted in tables 1 and 2) all mice were treated for 4 days.

Experimental Results: A variety of abnormalities occurred in the offspring of treated females. Many of them need to be examined histologically for their proper evaluation. Pending a thorough histologic and embryologic study of the material, the presence or absence of cleft palate has been chosen as the characteristic most suitable for statistical analysis, since it is so easily diagnosed. Table 1 presents the data for each strain treated at various stages of gestation and with various doses.

At the present stage of progress the numbers involved in each category of table 1 are, in most cases, too small to permit any valid conclusions to be drawn. However, it is apparent on scanning table 1 that the strains used fall naturally into two groups. Treated females of strains A and N produced relatively more defective offspring than treated females of strains C57, B and H. This difference was apparent in the early stages of the experiment. In table 2 the results for strains A and N have been lumped and compared with the combined results for strains C57, B and H. In addition the results for litters treated with daily doses of cortisone 1.25 and 2.5 mg., being similar, were combined. Extending the period of treatment to five days made no appreciable difference in the results, and so these litters have also been included in tables 1 and 2.

Where treatment was begun before the 10th day of gestation the number of treated females is as yet too few in number to be significant. When treatment was started on the 10th or 11th day, the incidence of cleft palate in the offspring was 79% in strains A and N and 21% in strains C57, B and H. For treatment started on the 12th or 13th day, the corresponding values were 29% and 8%, respectively, and when treatment was started on the 14th to 17th day they were 29% and 3%, respectively. It is therefore apparent that strains A and N differ from strains C57, B and H in their reaction to cortisone as measured by the incidence of cleft palates in the offspring of treated mothers.

In the relatively few cases where females were treated with 5 or 10 mg./day of cortisone the same trend occurred. In the susceptible strains there was resorption of the litter in the majority of pregnancies and a high incidence of cleft palates in the few litters that survived. In the relatively resistant strains these dosages caused very few resorptions or cleft palates in the offspring.

Effect of Dose: There was a clearcut relationship between the dosage of cortisone and the incidence and severity of defects in the offspring. As mentioned above, doses of 5 mg. or more daily usually caused intrauterine death and resorption of the embryos in the susceptible strains (table 1). With 2.5 or 1.25 mg./day for four days there were only two cases of a litter being resorbed, and the incidence of cleft palate ranged from 79% to 29% in the susceptible strains depending on the gestational stage at which treatment was started (table 2). Table 1 shows that the smallest dose used, 0.625 mg./day for four days, given to females of strains A and N at susceptible gestational stages produced no cleft palates in a total of 37 young. The same dose in mice of resistant strains produced no cleft palates in a total of 8 young.

Relation to Gestational Stage Treated: Table 2 shows that the later in gestation the injection of cortisone is begun, the less effective it is in causing cleft palates. It is interesting to note, however, that an appreciable number of cleft palates were found when treatment was started after the twelfth day (when the naso-maxillary fissure is said to have closed),[31] and a few cleft palates have been found in litters in which treatment was started as late as the sixteenth or seventeenth day of gestation. In general, the earlier treatment was started the more severe were the defects observed.

Defects Other Than Cleft Palate: As previously mentioned, a number of defects other than cleft palate were noted in the offspring of treated mice. These will be described in detail in a later publication. They included five cases of cleft "lip" and palate similar to the "spontaneous" cases which occur occasionally in the offspring of untreated animals. These cases have been excluded from the data, since the authors have not yet observed enough of them to be able to assess their significance. Other defects observed include shortening of the head and shortening of the mandible and spina bifida. There was one monster with no eyes, mouth, vibrissae or pinnae.

In the susceptible strains treated with 1.25 or 2.5 mg./day of cortisone for four days there was a marked reduction in birth weight of the resulting offspring. Stillborn young were more likely to be malformed than the living young, but an appreciable number of young with cleft palates were born alive. However, they never survived more than 24 hours postpartum.

Maternal Effects: The injections of cortisone produced no obvious effects on the treated females at the time of treatment. However, 8 of the 16 females of strain N that were treated had a complete prolapsus uteri following parturition. This condition is extremely rare in untreated strain N females, and did not occur following treatment of females of other strains. No conclusions as to the significance of these findings can be reached at this time.

Control Data: It was necessary to rule out the possibility that agents other than cortisone in the preparation used could cause the observed defects. Therefore a number of mice were treated with the cortisone-free vehicle used in the Merck cortone® preparation. Treatment was given at highly susceptible stages and the amount of vehicle used was equal in volume to the most effective dose of the Merck cortisone preparation (2.5 mg.). No cleft palates were observed in a total of 38 offspring (table 3).

As an indication that the incidence of "spontaneous" cleft palate (without harelip) is very low, if not zero, there is now a total of 142 mice, examined specifically for this defect, which came from mothers that were not treated with effective doses of cortisone. This includes 59 offspring of untreated mice, 45 offspring of mice treated with cortisone 0.625 mg. and 38 offspring of mice treated with inert vehicle. This shows that the cleft

TABLE 3

ABSENCE OF CLEFT PALATE IN OFFSPRING OF PREGNANT MICE GIVEN 4 DAILY DOSES OF 0.1 CC. OF INERT CORTISONE "VEHICLE"

Strain	A and N		C57			T
Day of gestation treatment started	11	12	11	12	13	
No. of ♀ ♀ treated	2	1	1	1	1	6
Total number of young born	14	3	8	6	7	38
No. with cleft palate	0	0	0	0	0	0

palates found in the litters represented in tables 1 and 2 must have been due to the cortisone treatment.

DISCUSSION

The discovery that cortisone injected into pregnant mice will produce congenital defects in the offspring adds another to the rapidly growing list of agents which will cause intrauterine developmental disturbances in mammals. Cortisone is known to have manifold effects on the mammalian organism. Among other things it can cause hyperglycemia, glycosuria, and an increase in the urinary excretion of nitrogen, potassium, sodium and chlorides[32-34] and (in rabbits) a marked lipemia.[35] The effects on the basal metabolic rate is variable and appears to depend on the balance between a calorigenic action and a thyroid-suppressing action via the pituitary.[36] The administration of cortisone depresses adrenal cortical function,[32] and suppresses the formation of connective tissue.[37] ACTH produces similar results.[32] It is as yet impossible to say which of these, or other actions of cortisone is related to the production of congenital defects. This will be investigated by studying the effects of concurrent administration of various agents with cortisone on the incidence of defects.

The various forms of maternal insult that cause congenital defects in the offspring can be regarded as forms of stress, and the possibility must be considered that they produce their effects on the offspring by causing the mother's adrenal to produce excessive amounts of cortisone-like compounds. Experiments are now in progress to see if ACTH or compound F will produce congenital defects in the same way that cortisone does. In deciding how far these findings in mice may apply to human congenital defects, it will be important to know whether cortisone and the naturally produced adrenal corticoids will cross the human placenta. This question, as far as is known, has not been settled yet.

The later in gestation that treatment was started, the fewer defects were observed. This is in accord with the observations of many workers who have found that certain developmental stages are particularly sensitive to certain agents. However, the fact that cleft palates were found in the offspring of mice treated anywhere from the ninth to the seventeenth day shows that the effect is not limited to a time when some special embryologic event is happening. Since some cleft palates are produced by treatment well after the stage when the naso-maxillary fissure is said to have closed (the twelfth day[31]) it seems that in these cases the defect may be due not to a delay in a developmental process but to a degenerative change. Further discussion of this problem will await embryologic analysis of this material.

SUMMARY

It has been shown that cortisone, injected into pregnant female mice, will produce cleft

palate and other congenital malformations in the resulting young. The incidence of cleft palate varies according to the genetic constitution of the treated mice, the dosage of cortisone used and the gestational stage at which treatment is begun.

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REFERENCES

1. Hale, F., Relation of vitamin A to anophthalmos in pigs, Am. J. Ophth. **18**:1087, 1935.
2. Warkany, J., and Nelson, R. C., Appearance of skeletal abnormalities in offspring of rats reared on deficient diet, Science **92**:383, 1940.
3. Warkany, J., Nelson, R. C., and Schraffenberger, E., Congenital malformations induced in rats by maternal nutritional deficiency. III. Malformations of extremities, J. Bone & Joint Surg. **25**:261, 1943.
4. Warkany, J., Nelson, R. C., and Schraffenberger, E., Congenital malformations induced in rats by maternal nutritional deficiency, Am. J. Dis. Child. **65**:882, 1943.
5. Warkany, J., and Schraffenberger, E., Congenital malformations induced in rats by maternal vitamin A deficiency. I. Defects of eye, Arch. Ophth. **35**:150, 1946.
6. Warkany, J., and Roth, C. B., Congenital malformations induced in rats by maternal vitamin A deficiency. II. Effects of varying preparatory diet upon yield of abnormal young, J. Nutrition **35**:1, 1948.
7. Warkany, J., Experimental studies on nutrition in pregnancy, Obst. & Gynec. Surv. **3**:693, 1948.
8. Wilson, J. G., and Warkany, J., Malformations in genito-urinary tract induced by maternal vitamin A deficiency in rat, Am. J. Anat. **83**:357, 1948.
9. Wilson, J. G., and Warkany, J., Aortic-arch and cardiac anomalies in offspring of vitamin A deficient rats, Am. J. Anat. **83**:113, 1949.
10. Wilson, J. G., and Warkany, J., Cardiac and aortic arch anomalies in offspring of vitamin A deficient rats correlated with similar human anomalies, PEDIATRICS **5**:708, 1950.
11. Andersen, Dorothy H., Effect of diet during pregnancy upon incidence of congenital diaphragmatic hernia in rat, Am. J. Path. **25**:163, 1949.
12. Warkany, J., Congenital malformations induced by maternal nutritional deficiency, J. Pediat. **25**:476, 1944.
13. Warkany, J., and Schraffenberger, E., Congenital malformations induced in rats by maternal nutritional deficiency. VI. Preventive factor, J. Nutrition **27**:477, 1944.
14. Giroud, A., and Boisselot, J., Répercussions de l'avitaminose B_2 sur l'embryon du rat, Arch. franç, pédiat. **4**:1, 1947.
15. Giroud, A., and Boisselot, J., Fente du palais et raccourcissement de la mandibule par avitaminose B_2, Rev. de stomatol. **49**:377, 1948.
16. Boisselot, J., Malformations congénitales provoquées chez le rat par une insuffisance en acide pantothénique du régime maternal, Compt. rend. Soc. de biol. **142**:928, 1948.
17. Boisselot, J., Malformations foetales par insuffisance en acide panthothénique, Arch. franç. pédiat. **6**:225, 1949.
18. Richardson, L., and Hogan, A. G., Diet of mother and hydrocephalus in infant rats, J. Nutrition **32**:459, 1946.
19. Richardson, L. R., and DeMottier, J., Inadequate maternal nutrition and hydrocephalus in infant rats, Science **106**:644, 1947.
20. Russell, L. B., X-Ray induced developmental abnormalities in mouse and their use in analysis of embryological patterns. I. External and gross visceral changes, J. Exper. Zool. **114**:545, 1950.
21. Warkany, J., Etiology of congenital malformations, in Advances in Pediatrics, edited by S. Z. Levine et al., New York, Interscience Publishers, Inc., 1947, vol. 2, p. 1.

22. Warkany, J., and Schraffenberger, E., Congenital malformations induced in rats by roentgen rays, Am. J. Roentgenol. **57**:455, 1947.
23. Hicks, S. P., Acute necrosis and malformation of developing mammalian brain caused by X-ray, Proc. Soc. Exper. Biol. & Med. **75**:485, 1950.
24. Ingalls, T. H., Curley, F. J., and Prindle, R. A., Anoxia as cause of fetal death and congenital defect in mouse, Am. J. Dis. Child. **80**:34, 1950.
25. Gillman, J., Gilbert, C., and Gillman, T., Preliminary report on hydrocephalus, spina bifida and other congenital anomalies in rat produced by trypan blue, South African J. M. Sc. **13**:47, 1948.
26. Haskin, D., Some effects of nitrogen mustard on development of external body form in fetal rat, Anat. Rec. **102**:493, 1948.
27. Tedford, M. D., and Risley, P. L., Desoxycorticosterone and pregnancy in ovariectomized hamsters, Anat. Rec. **108**:108, 1950.
28. Baxter, H., and Fraser, F. C., Production of congenital defects in offspring of female mice treated with cortisone, McGill M. J. **19**:245, 1950.
29. Fraser, F. C., Experimental production of congenital anomalies, Canad. M. A. J. **64**:270, 1951.
30. Snell, G. D., and others, Biology of Laboratory Mouse, Philadelphia, The Blakiston Company, 1941.
31. Gruneberg, H., Development of some external features in mouse embryos, J. Hered. **34**:89, 1943.
32. Sprague, R. G., and others, Observations on physiological effects of cortisone and ACTH in man, Arch. Int. Med. **85**:199, 1950.
33. Ingle, D. J., Production of glycosuria in normal rat by means of 17-hydroxy-11-dehydrocorticosterone, Endocrinology **29**:649, 1941.
34. Brown, J. S. L., Johnson, L. G., Schenker, V., and Venning, E. H., Protein metabolism in acute and chronic disease and relation of protein metabolism in acute and chronic disease and relation of protein metabolism to excretion of gluco-corticoids, in the Proceedings of the Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, p. 108.
35. Rich, A. R., Cochran, T. H., and McGoon, D. C., Marked lipemia resulting from administration of cortisone, Bull. Johns Hopkins Hosp. **88**:101, 1951.
36. Hill, S. R., Reiss, R. S., Forsham, P. H., and Thorn, G. W., Effect of adrenocorticotropin and cortisone on thyroid functions: Thyroid-adrenocortical interrelationships, J. Clin. Endocrinol. **10**:1375, 1950.
37. Ragan, C., and others, Effect of cortisone on production of granulation tissue in rabbit, Proc. Soc. Exper. Biol. & Med. **72**:718, 1949.

SPANISH ABSTRACT

Producción de Defectos Congénitos en la Descendencia de Ratones Embarazadas Tartadas con Cortisona

Se demostró que la cortisona, inyectada a ratones hembras embarazadas, puede ocasionar labio leporino y otras malformaciones en los hijos resultantes. La incidencia del labio leporino varia de acuerdo con la constitución genética del ratón tratado, la dósis de cortisona empleada, y el periodo de gestación en el cual el tratamiento es comenzado.

1615 Cedar Avenue

PSEUDOCYST OF THE PANCREAS IN CHILDHOOD

By JAMES MITHOEFER, M.D.
Cooperstown, N.Y.

CYSTS of the pancreas are rare in childhood and of those which have been observed, pseudocysts are among the least common. Because of the rarity of this lesion, the present case is reported.

REPORT OF CASE

A 20 mo. old girl was admitted to the Cincinnati Children's Hospital with a chief complaint of swelling of the abdomen.

The present illness began 3 mo. before when progressive enlargement of the abdomen accompanied by low grade fever was noted. At that time no other symptoms were reported. She was admitted to another hospital where the sole physical abnormality was ascites. Three tuberculin patch tests were said to be negative. Abdominal paracentesis yielded 6 l. of brown fluid which contained lymphocytes and neutrophils; no tumor cells were seen. Laparotomy was performed at the other hospital. The surgeon reported that there was generalized peritonitis and that the entire intestine was covered by filmy adhesions. The parietal peritoneum was markedly thickened. Gauze-like adhesions extended over the dome of a liver of normal size. No tumors, cysts or masses were seen. A diagnosis of tuberculous peritonitis was made. The wound healed without incident. Postoperatively the patient received streptomycin therapy, and abdominal paracentesis was performed at weekly intervals until her admission to the Children's Hospital. During the month before admission the patient became progressively more lethargic and irritable. Her appetite remained fairly good, but there was marked wasting.

The family history was not contributory. One of her 5 siblings died in early childhood of malnutrition, rickets and pneumonia.

Past history was unrevealing except that 5 mo. before her illness began she had fallen from a porch. Shortly thereafter she began to have crampy abdominal pain and fever. She had been admitted to a hospital in another city, received a blood transfusion, and had been discharged after a few days with a diagnosis of bronchopneumonia and pyelitis.

Examination showed an emaciated child who weighed 13.2 kg. and appeared to be chronically ill. The inguinal, axillary and cervical lymph nodes were easily palpable but not remarkably enlarged. The abdomen was hugely distended and presented signs of free peritoneal fluid (Fig. 1). No viscera or other masses were palpable. Distention of the superficial veins of the abdomen was noted. There was a left indirect inguinal hernia containing fluid. No other significant abnormality was present.

Laboratory work on admission showed: Hgb. 11.7 gm./100 cc.; WBC 15.9 thousand/cmm. with an essentially normal differential count. The urine contained + albumin and +++ acetone, but was otherwise normal. Erythrocyte sedimentation rate was 35 mm./hr. corrected; prothrombin time 15.8 sec., control 19.3; blood NPN 27 mg./100 cc. Examination of the serum revealed: CO_2 content, 22.9 mM./1.; chloride, 109 mEq./1,; calcium, 8.7 mg./100 cc.; inorganic phosphorus, 4.5 mg./100 cc.; phosphatase, 8.1 Bodansky units; bilirubin, 0.25 mg./100 cc.; cholesterol, 178 mg./100 cc.; amylase, 320 Somogyi u.; protein, 5.5 gm./100 cc., of which 3.4 gm. were albumin and 2.1 gm. were globulin. A glucose tolerance test produced a normal curve. During the hospital course there was slight but insignificant variation in these values.

Abdominal fluid was aspirated on many occasions. It contained 2.0 gm./100 cc. protein, 110.4 mEq./l. chloride and 3200 Somogyi u. of amylase. No organisms were seen on several direct smears and none was grown on culture. Neither of 2 inoculated guinea pigs developed tuberculosis. Examination of the centrifuged sediment of the abdominal fluid showed fragments of collagenous tissue and a

From the Department of Surgery of the College of Medicine of the University of Cincinnati and the Children's Hospital of Cincinnati.

(Received for publication May 4, 1951.)

moderate number of histiocytes, the cytoplasm of which contained blood pigment. No tumor cells were seen.

Roentgen examination of the thorax showed marked elevation of both diaphragms with compression of the lungs. The abdomen was greatly increased in size and of a uniform density, an appearance consistent with intraperitoneal fluid. Examination of the gastrointestinal tract showed the stomach to be displaced upward, to the right, and anteriorly. The duodenal loop was greatly widened. The ascending and transverse portions of the colon were displaced anteriorly. The space between colon and stomach was occupied by a large homogeneous mass of "water density." Retrograde pyelograms

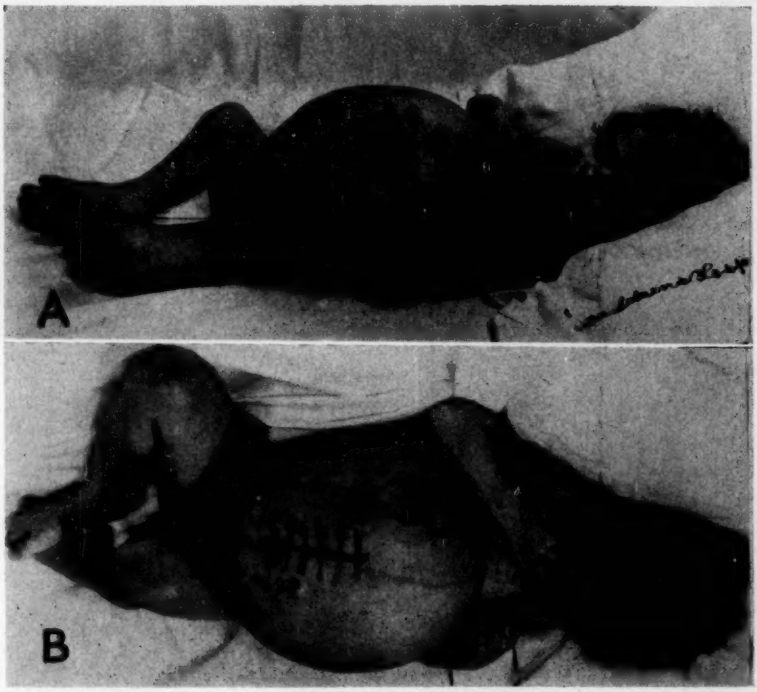

FIG. 1. Appearance of patient at time of admission. Abdominal distention represents pancreatic pseudocyst. Only small amount of free peritoneal fluid was present. Abdominal scar resulted from laparotomy at another hospital 6 wk. before.

showed inferior displacement of the left kidney but no anterior displacement. Pyelo-canalicular backflow was observed (Fig. 2).

A diagnosis of pseudocyst of the pancreas was made, and 3 wk. after admission, the abdomen was opened through a 5 cm. transverse incision in the left upper quadrant. There was a small amount of clear peritoneal fluid. Immediately beneath the incision lay the dome of a tensely filled cyst, estimated to be 18 cm. in diameter, which seemed to be presenting from behind the gastrocolic ligament. The accessible portion of the peritoneum and the bowel was not palpably abnormal. The cyst wall was sutured to the incised peritoneum and the wound was packed open. Two days later the cyst was opened with the release of a large amount of dark brown fluid. Palpation and inspection of the interior of the cavity revealed that the stomach formed its superior surface, the transverse colon and mesocolon its inferior surface, and the pancreas its base. The pancreas was somewhat firmer than usual and in the region of the tail of the pancreas there was a 3 cm. area which was roughened and denuded of peritoneum. A biopsy of the wall of the cyst showed nonspecific chronic granulomatous inflammation of adipose tissue.

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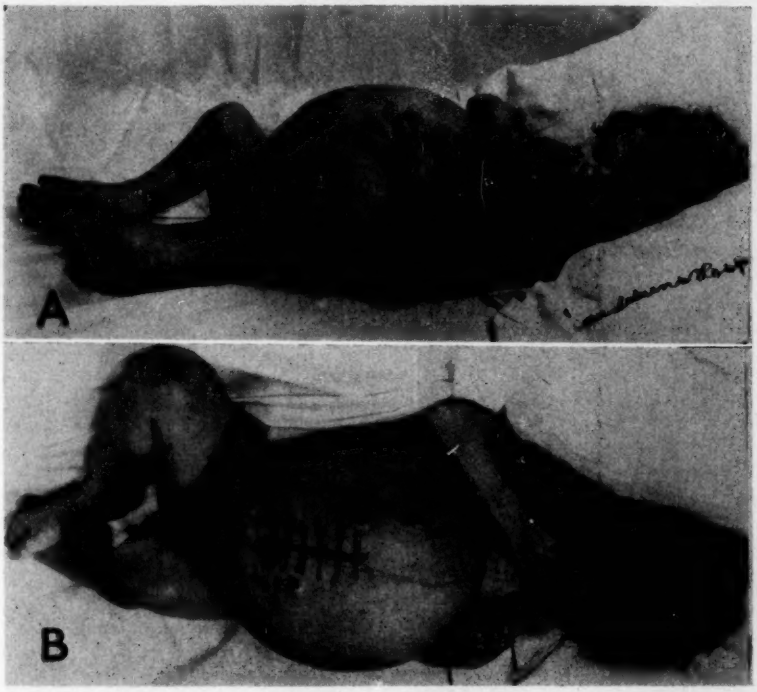

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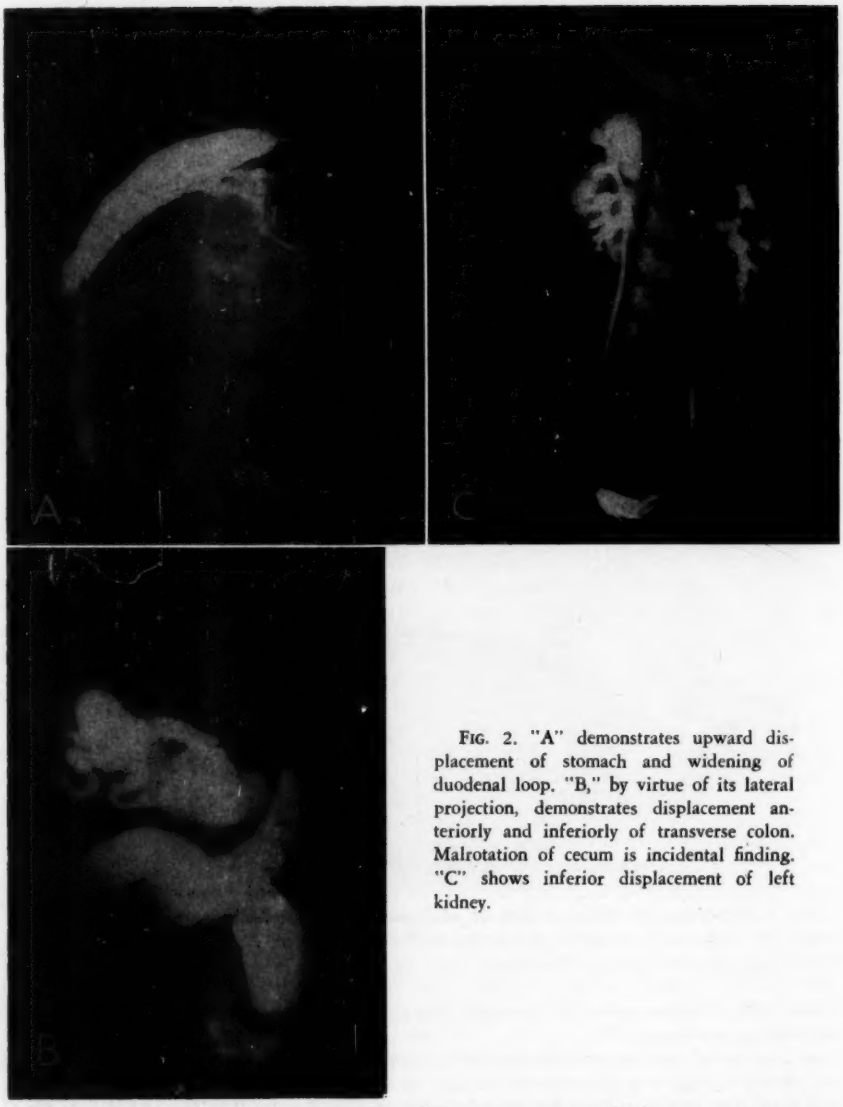

FIG. 2. "A" demonstrates upward displacement of stomach and widening of duodenal loop. "B," by virtue of its lateral projection, demonstrates displacement anteriorly and inferiorly of transverse colon. Malrotation of cecum is incidental finding. "C" shows inferior displacement of left kidney.

The patient's postoperative course was complicated by an upper respiratory tract infection and otitis media. Otherwise, recovery was steady and relatively rapid. The sinus tract in the wound drained a moderate amount of serosanguineous fluid. The patient was discharged from the hospital 7 wk. after operation with a rubber catheter in the wound. A small amount of drainage continued for 7½ wk. when the catheter was removed for cleaning and could not be reinserted. The wound healed completed a few days thereafter (Fig. 3).

Barium enema 1 mo. later showed no abnormality in the position of the intestinal tract. The upper urinary tract was not re-examined.

When last seen, 10 mo. after operation, she was entirely asymptomatic. The wound was solidly healed. No abdominal mass was palpable.

Review of the Literature

Many general reviews of the subject of pseudocyst of the pancreas in adults are available[1–14] so that only a brief description of its nature will be given in this report. Numerous classifications of pancreatic cysts may be found. One of the simplest is that given by Priestley,[15] a modification of which follows:

Pseudocyst is so termed because it has no true epithelial lining and is composed of granulation tissue in varying stages of development surrounding the more or less liquid products of pancreatic destruction and fat necrosis.

Retention cyst results from long standing partial obstruction of a major pancreatic duct. It has a lining of duct epithelium and is usually the result of obstruction by stone or fibrosis secondary to chronic pancreatitis.

Neoplastic cysts are all comparatively rare and are usually found to be (1) benign cystadenoma, (2) cystadenocarcinoma, (3) dermoid cyst or (4) teratoma.

Congenital cyst presents neither a neoplastic element nor a retention factor. It is generally associated with polycystic disease elsewhere.

Parasitic cyst caused by echinococcus infestation is rarely encountered in this country.

Fibrocystic disease of the pancreas is not manifested by gross cyst formation. Because

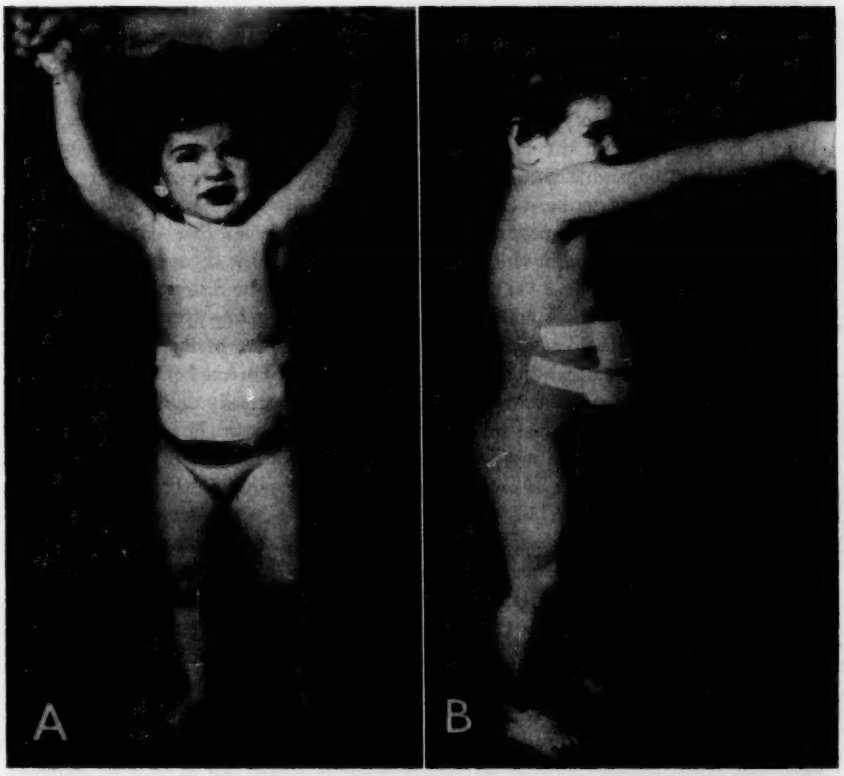

FIG. 3. Appearance of child 3 mo. after definitive therapy. Wound healed and dressing was discarded soon thereafter.

of the small size of the cystic spaces in this lesion and the widespread systemic manifestations of the disease, it is not a problem in differential diagnosis of pancreatic tumors.

Pseudocyst of the pancreas is most often observed following interstitial or hemorrhagic pancreatitis; it may occur as the result of biliary tract disease or blunt trauma to the upper abdomen. It has not been observed following the pancreatitis associated with epidemic parotitis. The essential train of events stems from necrosis of the gland substance with release of activated trypsinogen and lipase into the lesser omental bursa or between the leaves of the transverse mesocolon. There ensues a chemical inflammation of the peritoneal surfaces and the retroperitoneal tissue with fat necrosis and tissue autolysis. The resultant mass of liquefied material is ultimately encapsulated by granulation tissue and any adjacent viscera. The regional anatomy then determines the progress of the lesion. In most cases the process develops in the lesser omental bursa and presents anteriorly through the gastrocolic omentum. If it dissects between the leaves of the transverse mesocolon, it may penetrate the wall of the colon or it may present as a mass pushing the transverse colon cephalad. In rare instances the process may migrate down either of the lateral paracolic spaces to present as a mass in the flank or in the pelvis.

The thickness and structure of the cyst wall depends on its age. Similarly, the contents of the cyst vary from semisolid, grumous material in relatively new cysts, to clear thin fluid in those of long standing. Whatever color the fluid may have is the result of degradation of hemoglobin. Because of the productive inflammatory reaction, pseudocysts are invariably adherent to contiguous structures.

The diagnosis of pseudocyst of the pancreas can be made if one is aware of the possibility of its occurrence in the presence of an upper abdominal mass. A history of a preceding illness compatible with pancreatitis or of upper abdominal trauma is of confirmatory value, but may not be elicited. The cyst itself is often asymptomatic. Its presence rarely causes mechanical obstruction to a hollow viscus. Melena has been noted infrequently since the wall of the intestine is rarely penetrated by the digestive process. Most of the cysts, however, produce vague upper abdominal pain or distress. Severe pain or radiation of pain to the back is unusual, but may be the presenting symptom.

The findings on physical examination depend on the location of the cyst and its size. It is usually deeply seated and therefore has poorly defined borders because of the overlying viscera. As the mass becomes larger it may be more easily delineated and as it approaches the anterior abdominal wall, it becomes palpably cystic. Because of fixation to the retroperitoneal tissues, the cysts are ordinarily not movable either manually or by descent of the diaphragm, but, if located in the tail of the pancreas, they may be moved in a ventral direction.

Roentgen examination may be of the utmost value in establishing a diagnosis of pseudocyst of the pancreas inasmuch as the location of the tumor can be determined by the displacement of the various related abdominal viscera. The stomach is usually displaced superiorly and anteriorly and the transverse colon inferiorly and anteriorly. If the cyst is large enough or is located in the head of the pancreas, the duodenal loop may be widened. There is usually no displacement of the kidneys, although an unusually large mass may depress the left kidney.

There are no consistently positive laboratory findings in this condition. The hemoglobin concentration and plasma proteins may be diminished if the cyst is of long standing and has interfered, by the production of anorexia, with nutrition. The serum amylase is

not elevated unless there is coexistent pancreatitis. It is unusual to encounter sufficient destruction of pancreatic tissue to result in insulin deficiency. Aspiration of the contents of the cyst is usually ill-advised, but if it is done, the fluid may be either clear or dark. The amylase activity of the cyst fluid is usually high; in very old cysts it may not be demonstrable.

The incidence of pancreatic pseudocyst is relatively high in adults. Judd, Mattson and Mahorner[2] were able to find 47 cases in the files of the Mayo Clinic from 1907 to 1931. Adams and Nishijima[3] reported nine cases seen at the Lahey Clinic between 1926 and 1945. Siler and Wulsin[14] found 14 cases of pseudocyst at the Cincinnati General Hospital complicating 111 admissions for acute pancreatitis. Meyer[7] was able to collect 269 cases in an extensive review of the literature.

This condition is primarily an affliction of the fourth and fifth decades, although it may occur at any age. In each of the recently reported series, the youngest recorded was in the neighborhood of 20 years. The condition is extremely rare in infancy and childhood. The literature contains six case reports of pancreatic cysts in children. Of these, four[16–19] cannot be classified as pseudocyst because of their gross appearance and in one of these[17] because of the microscopic demonstration of an epithelial lining.

The remaining two constitute the only acceptable cases of pseudocyst of the pancreas in childhood. In 1925 McWhorter[18] collected 19 cases of pancreatic cyst and pseudocyst which had been seen by the members of the Chicago Surgical Society. He mentioned briefly a six year old boy whose abdomen was run over by a wagon. Two weeks later he developed an asymptomatic cystic mass in the upper abdomen which was drained of about 300 cc. of fluid. The wound healed in about five weeks. Fifteen years later there had been no recurrence.

Drennan[20] reported that a four year old boy presented himself with an orange-size tumor in the epigastrium some six weeks after he had been run over by the rear wheel of a wagon. This proved to be a cyst in the region of the pancreas. It was drained surgically. The fluid contained "pancreatic ferments" and a biopsy of the adherent omentum showed fat necrosis.

Discussion

A review of the literature and the author's experience indicates that pseudocyst of the pancreas rarely occurs in childhood. At the Cincinnati Children's Hospital there were 101,960 admissions between January 1, 1928 and January 1, 1951. The diagnosis of acute pancreatitis was not recorded during that time, except as it occurred in association with epidemic parotitis. The present case was the only instance of pseudocyst observed. Of the previously reported cases of pancreatic cyst in children, all but two were almost certainly not pseudocyst.

This case seems to meet all the criteria required by the category of pseudocyst of the pancreas. The child had a fall from a porch eight months before definitive operation. Within a few days a febrile prostrating illness accompanied by abdominal pain supervened. This was thought to be bronchopneumonia. The roentgen films of the thorax made at that time were not available, but it seems possible that a paramediastinal shadow, so often seen with acute pancreatitis, might have been mistaken for pneumonitis. Furthermore, it would seem unusual to give a blood transfusion to a patient with bronchopneumonia not severe enough to require more than a few days of hospitalization. Such treatment might well have been necessary if the child had acute pancreatitis secondary to

abdominal trauma. After an interval of six months, abdominal swelling appeared and led to laparotomy. The surgeon's impression of "tuberculous peritonitis" in the light of subsequent developments probably represented misinterpretation of peritoneal reaction to fat necrosis secondary to underlying pancreatitis. The location of the cyst at the last operation, the character of its contents, and the histologic structure of its wall are entirely in keeping with the diagnosis of pancreatic pseudocyst. One may question the relationship of the trauma eight months earlier to the pancreatitis, but we have no other explanation for formation of the cyst. It is of interest that Priestley reports that in 44 cases of pseudocyst a history of pancreatitis was present in 21 instances and trauma in two.[15] The importance of blows and crushing injuries in the pathogenesis of pseudocysts has been emphasized by others.[8,21] In children, because of the infrequency of associated biliary tract disease, some sort of mechanical injury almost always precedes the onset of symptoms. Certainly this has been the case in the two previously reported cases.

The preoperative diagnosis was suggested in this case by the radiologist's demonstration of a space-consuming lesion in the region of the pancreas and was confirmed by the demonstration of amylase in the cyst fluid. Observations at the time of laparotomy confirmed the clinical impression.

Summary

The literature pertaining to pseudocyst of the pancreas is reviewed briefly. The third authenticated case of pseudocyst of the pancreas in childhood is reported.

References

1. Gordin, A. E., Pancreatic cysts, Ann. Surg. **106**:1095, 1937.
2. Judd, E. S., Mattson, H., and Mahorner, H. R., Pancreatic cysts, Arch. Surg. **22**:838, 1931.
3. Adams, R., and Nishijima, R. A., Surgical treatment of pancreatic cysts, Surg., Gynec. & Obst. **83**:181, 1946.
4. Pinkham, R. D., Pancreatic collections (pseudocysts) following pancreatitis, Surg., Gynec. & Obst. **80**:225, 1945.
5. Rabinovitch, J., and Pines, B., Cysts of pancreas, Arch. Surg. **45**:727, 1942.
6. Von Koerte, W., Zur Behandlung der Pancreaszysten und -pseudozysten, Deutsch. Med. Wchnschr. **37**:536, 1911.
7. Meyer, K. A., Sheridan, A. I., and Murphy, R. F., Pseudocysts of pancreas, Surg., Gynec. & Obst. **88**:219, 1949.
8. Lloyd, J., Injury to pancreas: Cause of effusion into lesser peritoneal cavity, Brit. M. J. **2**:1051, 1892.
9. Chesterman, J. F., Treatment of pancreatic cysts, Brit. J. Surg. **30**:234, 1943.
10. McWhorter, G. L., Cysts of pancreas, Arch. Surg. **11**:619, 1935.
11. Carter, R. F., and Slattery, L. R., Management of pancreatic cysts, S. Clin. North America **27**:411, 1947.
12. Friedenwald, J., and Cullen, T., Pancreatic cysts with report of seven cases, Am. J. M. Sc. **172**: 313, 1926.
13. Einhorn, M., On pancreatic cysts, Am. J. M. Sc. **169**:389, 1925.
14. Siler, V. E., and Wulsin, J. H., Acute pancreatitis, J.A.M.A. **142**:78, 1950.
15. Priestley, J. T., Surgical lesions of pancreas, S. Clin. North America **30**:971, 1950.
16. Eha, C. E., Case of congenital cyst of pancreas, J.A.M.A. **78**:1294, 1922.
17. Telling, W. H. M., and Dobson, J. F., Pancreatic cyst in infant, Brit. J. Child. Dis. **6**:202, 1909.
18. Connolly, D. I., Note on case of pancreatic cyst in child aged fourteen months, Lancet **1**:803, 1911.
19. Railton, T. C., Case of pancreatic cyst in infant, Brit. M. J. **2**:1318, 1896.

20. Drennan, E., Traumatic pancreatitis, Ann. Surg. **76**:488, 1922.
21. Koucky, J. D., Beck, W. C., and Todd, M. C., Perforation of pancreatic pseudocysts, Surg., Gynec. & Obst. **73**:113, 1941.

SPANISH ABSTRACT

Pseudoquístes del Pancreas en la Niñez

Debido a la rareza de pseudoquistes del pancreas en la niñez, se reporta el siguiente caso, primero entre 101,960 ingresos en el Cincinnati Children's Hospital.

Una niña de 20 meses de edad fué ingresada en el hospital con su abdomen enormemente distendido por un pseudoquíste del pancreas. Cinco meses antes del inicio del aumento de tamaño de su abdomen, el paciente tuvo una enfermedad, la cual de acuerdo con los acontecimientos posteriores creemos fué una pancreatitis traumática. El diagnóstico de pseudoquíste del pancreas fué sugerido por la demostración radiológica de una masa retroperitoneal, la cual desplazaba el estómago hacia arriba y anteriormente, ampliaba el marco duodenal, desplazaba las porciones ascendente y transversa del colon anteriormente y al riñon izquierdo inferiormente. Esta impresión fué confirmada por la demostración de 3200 unidades Somagyi de amilasa en el liquido del quiste y 320 unidades en el suero. El pseudoquíste fué marsupializado y cuando fué quirurgicamente expuesto se encontró que se originaba de la cola del pancreas. Cuando el paciente fué visto diez meses después de la operación estaba completamente asintomatico. El abdomen era de tamaño normal y no pudo demostrarse tumoración al exámen fisico o por el enema de bario. La herida habia cicatrizado firmemente a los siete meses de la operación.

Una revisión de la literatura muestra que entre los muchos casos reportados, solamente pudieron encontrarse dos casos autenticos de pseudoquístes ocurridos en la niñez; en cada uno de ellos, la lesión se desarrolló después de traumatismos severos, no penetrantes, del abdomen superior.

Se ofrece una clasificación de los quístes pancreaticos. Se discute la patogénesis y el diagnóstico diferencial de los pseudoquístes. Se presentan fotografías mostrando el paciente en el momento de su ingreso en el hospital, y después de su curación. Se reproducen las radiografías realizadas en este paciente.

The Mary Imogene Bassett Hospital, Cooperstown, N.Y.

CONGENITAL MEGACOLON (HIRSCHSPRUNG'S DISEASE)

Follow-up on Eighty-two Patients Treated Surgically

By ORVAR SWENSON, M.D.
Boston

A NEW concept of the pathology and surgical treatment of congenital megacolon has been published.[1-4] The pathology was described as absence of ganglion cells in Auerbach's plexus in the rectosigmoid and rectum. This segmental congenital defect in the myenteric plexus was postulated to account for the absence of peristalsis in the distal colon. Surgical resection of the functionally defective bowel relieved these patients. The following clinical experiences and experiments sustain this concept.

Colostomy above the rectosigmoid in four patients with congenital megacolon relieved abdominal distention and colonic stasis. Six months after colostomy closure, these four patients, in whom rectosigmoid resection was not performed, suffered a complete recurrence of the disease. Reopening the colostomy in these patients again relieved all their symptoms with return of the colon to approximately normal size. The dilatation and hypertrophy of the colon seem to have been secondary to a functional obstruction in the rectum and rectosigmoid.

Tracings of large bowel peristalsis were made to determine the nature of the rectosigmoid dysfunction. Three small rubber tubes with balloons attached were inserted through a transverse colostomy and positioned so that one balloon was at the splenic flexure, one in the descending colon, and one in the rectosigmoid. The balloons were inflated with 10 cc. of air and attached to recording manometers. Normal recordings were secured from two patients who had transverse colostomy as a result of right colectomy for gangrenous intussusception. The kymograph tracings showed a progression of the peristaltic waves from the transverse colon to the anus. Identical studies on five patients with congenital megacolon and transverse colostomy showed normal peristalsis in the dilated and hypertrophied colon, but in no instance did these peristaltic waves progress into the rectosigmoid. From this part of the colon the balloon recorded only slight contractions, a fraction of the amplitude of, and entirely unrelated in timing to the normal peristaltic waves in the proximal colon.

Histologic examination of the rectosigmoid surgically removed from patients with congenital megacolon has demonstrated an absence of ganglion cells in Auerbach's plexus. Similar findings have been reported by other investigators.[5-8] Experimental destruction of myenteric plexus was performed by Cannon to determine the role of the ganglion cells in the reflex. Segments of intestine treated in such a manner lost their peristaltic function.[9] This experimental situation may be analagous to congenital megacolon where the congenital failure of ganglion cells to develop may account for the absence of peristalsis in the rectosigmoid.

Previous types of colonic resections have proved unsatisfactory in the experience of

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many surgeons. Among these are Barrington-Ward,[10] who reported a 25% recurrence rate, and Ladd[11] who had some gratifying early results, similar to those recently reported by Ritter,[12] only to have the late results (years afterward) prove so unsatisfactory that he abandoned the operation.

Selection of Patients for Surgical Treatment

Benefit from this new surgical treatment can be assured only by a rigid selection of patients. Enlargement of the colon alone, regardless of degree, was not pathognomonic of congenital megacolon but may often prove to be the result of anal stricture, tumors or chronic constipation. The various mechanical obstructions were readily detected by physical examination and from barium enema studies. The differential diagnosis of chronic constipation and congenital megacolon was in some instances difficult. However, in chronic constipation the history was often short and on examination there was usually a rectal fecal impaction. The history of constipation in congenital megacolon usually dated from birth and abdominal distention was marked, with fecal impactions in the sigmoid.

A certain diagnosis of congenital megacolon can be made only by the use of a barium enema. This roentgen examination often proved difficult to perform and the following precautions were taken to facilitate the procedure: A small quantity of barium was used to preclude complete filling of the dilated and redundant sigmoid which would obscure the outline of the narrow rectosigmoid. The most satisfactory fluoroscopic view of the rectosigmoid was gained with the patient in oblique position. Often it was necessary to push on the lower abdomen and thus to manipulate the sigmoid out of the pelvis as the patient was maintained in Trendelenburg position. These maneuvers helped to secure a good view of the irregular narrow rectosigmoid and the funnel-shaped enlargement into the dilated sigmoid, which was the pathognomonic finding in congenital megacolon (Fig. 1).

When the dilatation extended down to the anal sphincter and there was good evacuation, a diagnosis of chronic constipation was made despite the degree of enlargement of the colon. Such patients were in most instances cured with low residue diets and careful habit training.

In newborn and young infants the diagnosis of congenital megacolon even by roentgenogram was difficult because dilatation of the colon was minimal and the abrupt change in caliber from the sigmoid to rectosigmoid was not present. Seven of the patients had normal barium enemas at birth but several months later developed the typical lesion in the distal colon. It was not unusual for a newborn infant with congenital megacolon to present the clinical appearance of small bowel obstruction with vomiting, abdominal distention and failure to pass meconium. A plain film in such patients showed a distended gas-filled intestinal loop and it was impossible to determine whether it was small or large bowel. In such questionable cases a barium enema identified the dilated loop with certainty, and avoided unnecessary exploration if it proved to be colon.

Once the diagnosis of congenital megacolon was made, the patient was prepared for a one stage resection, except in extremely sick patients with marked abdominal distention, when a preliminary colostomy was performed.

Preoperative Preparation and Postoperative Care

After the diagnosis was made, preoperative preparation during a 30 day period at home was arranged. A low residue diet, oral mineral oil and daily enemas are prescribed.

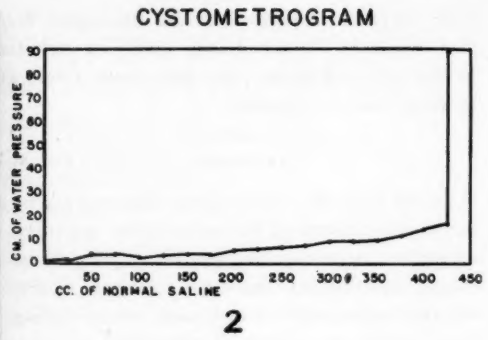

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FIG. 1. RG of lesion in congenital megacolon. Note narrow rectosigmoid with dilatation of sigmoid.

FIG. 2. Cystometrogram on 5 yr. old boy with congenital megacolon. Capacity is twice that of normal child of this age.

FIG. 3. Preoperative and 2 yr. postoperative barium enemas. Note colon is essentially negative. There is considerable filling of terminal ileum.

During the last 14 days of the preparation, sulfasuxidine was administered to secure a liquid fecal stream with low bacterial count.

Before operation a careful examination of the patient's urinary system was undertaken. Cystometrograms have shown that half the patients with congenital megacolon have atonic bladders with increased capacity (Fig. 2). This may be additional evidence of a congenital autonomic system defect.

Bladder examination should include a cystogram, a cystometrogram and the determina-

tion of residual urine. If preoperative examination was neglected and postoperative evidence of bladder dysfunction developed, the operative procedure could be unfairly blamed. Intravenous urograms were made to determine the condition of the ureters and renal pelvis.

Preoperative rectal irrigations were performed by inserting a large soft rectal tube through the narrow segment into the dilated colon. Occasionally it was necessary to do this with fluoroscopic aid, and on two occasions proctoscopy was resorted to. Once in position the tube was taped in place and washing of the colon was done three times a day. Two days of such decompression resulted in a scaphoid abdomen and the patient was ready for operation.

Resection of the rectum and rectosigmoid with a pull-through anastomosis was well tolerated by patients with congenital megacolon. This operation, which is complicated and difficult to perform, has been described in detail elsewhere.[4] It was essential to have an intravenous cannula tied in place so that blood could be administered as needed throughout the operation.

After operation gastric suction was maintained until peristalsis returned which usually took place in 24 to 48 hours. Fluids were given orally as soon as the tube was removed and in 2 or 3 days a full diet was usually tolerated.

Postoperatively, the bladder is drained by a urethral catheter for four days. During the next six days tidal irrigation was utilized. Then, if the cystometrogram was comparable to the preoperative examination, the catheter was removed. Patients were watched to see that urination took place four times a day and that before discharge residual urine was not excessive. Chemotherapy postoperatively consisted of crysticillin, 300,000 units daily, until the fourth to sixth postoperative day and gantrisin until four days after the bladder catheter was removed.

Some patients, particularly those below 3 years of age, became distended during the first 4 or 5 postoperative days. Treatment consisted of insertion of a large soft rectal tube and gentle washing of the colon with saline solution. Quantities of gas were released and the abdomen became soft and flat. After a few days spontaneous movements occurred and irrigations were discontinued. Such help was necessary in not more than 25% of the patients. The others began having spontaneous movements the third or fourth postoperative day.

Complications

In 82 cases there have been only four urinary complications. Two were mild infections due to premature discontinuation of chemotherapy. Two patients with large residuals were treated with tidal irrigations for a 10 day period, after which the residuals were normal.

Children under 3 years of age tend to have bouts of diarrhea months after operation. Twelve such patients had acute illnesses characterized by vomiting, severe diarrhea and abdominal distention with high fever. During such episodes the buttocks became excoriated, anal sphincter spasm developed and unless help was given, a severe illness ensued. The insertion of a large rectal tube and gentle washing of the colon with normal saline solution daily for 4 to 5 days resulted in dramatic cures. Vomiting stopped, the distention disappeared, and the infants began to have spontaneous daily movements. The author believes these attacks are acute gastrointestinal upsets due to a virus. This complication is not seen in the older patients.

There has been one recurrence in 82 patients. At operation this infant's colon presented no difference in caliber between normal and aganglionic bowel. Therefore, there was not the usual guide which establishes the proximal line of resection. Postoperatively this patient's symptoms did not improve and a second operation demonstrated an 8 cm. aganglionic segment which had been missed at the first procedure. Consequently, during the past year "rapid sections" have been made during operation to indicate the extent of the proximal aganglionic bowel and thus to insure its complete removal. This patient was one of two postoperative deaths in this series of 82 patients.

One 2½ year old child did not have regular movements until three months after operation. He was treated with irrigations during this period. He has now been followed two years and he has continued to do well, requiring no assistance.

Results

Sphincter function has been normal in all postoperative patients. Rarely slight soiling has occurred in the early postoperative period but subsided completely in 5 to 6 days.

Postoperatively abdominal distention has disappeared over a period of 6 to 8 months. All patients have gained in weight and their general growth has been normal. Diets are unrestricted and no mineral oil, laxatives or enemas are necessary. Barium enemas as early as the second postoperative months have shown an essentially normal colon (Fig. 3).

Eighty-two patients with congenital megacolon have been relieved of their symptoms by this new surgical technic, which consists of resection of the rectum and rectosigmoid without disturbing anal continence.

References

1. Swenson, O., and Bill, A. H., Jr., Resection of rectum and rectosigmoid with preservation of sphincter for benign spastic lesions producing megacolon, Surgery **24**:212, 1948.
2. Swenson, O., Neuhauser, E. B. D., and Pickett, L. K., New concepts of etiology, diagnosis and treatment of congenital megacolon (Hirschsprung's disease), Pediatrics **4**:201, 1949.
3. Swenson, O., Rheinlander, H. F., and Diamond, I., Hirschsprung's disease: New concept of etiology; operative results in thirty-four patients, New England M. J. **241**:551, 1949.
4. Swenson, O., New surgical treatment for Hirschsprung's disease, Surgery **28**:371, 1950.
5. Robertson, H. E., and Kernohan, J. W., Myenteric plexus in congenital megacolon, Proc. Staff Meet., Mayo Clin. **13**:123, 1938.
6. Tiffin, M. E., Chandler, L. R., and Faber, H. K., Localized absence of ganglion cells of myenteric plexus in congenital megacolon, Am. J. Dis. Child. **59**:1071, 1940.
7. Zuelzer, W. W., and Wilson, J. L., Functional intestinal obstruction on congenital neurogenic basis in infancy, Am. J. Dis. Child. **75**:40, 1948.
8. Bodian, M., Stephens, F. O., and Ward, B. C. H., Hirschsprung's disease and idiopathic megacolon, Lancet **1**:6, 1949.
9. Cannon, W. B., and Burket, I. R., Endurance of anemia by nerve cells in myenteric plexus, Am. J. Physiol. **32**:347, 1913.
10. Barrington-Ward, L. E., Congenital enlargement of colon and rectum, Brit. J. Surg. **1**:345, 1914.
11. Ladd, W. E., Megacolon, Boston M. & Surg. J. **174**:81, 1921.
12. Ritter, J. A., Hawthorne, H. R., and Metzger, H. N., Congenital megacolon: Report of three cases of "obstructive" type treated by resection of dilated segment in contrast to resection of distal narrowed segment, Pediatrics **5**:791, 1950.

Spanish Abstract

Megacolon Congénito (Enfermedad de Hirschsprung); Observaciones en 72 Pacientes Tratados Quirurgicamente

El concepto actual de la patología del megacolon congénito se basa en la ausencia de peristalsis en el rectosigmoide. La resultante obstrucción funcional de ésta region produce una dilatación y

hipertrofia del colon adyacente próximal. El rectosigmoide en esta enfermedad carece de las celulas nerviosas ganglionares del plexo de Auerbach. Debido a que este plexo ganglionar nervioso forma parte de la inervación parasimpatica de los nervios pelvicos, la ausencia de celulas ganglionares mioentericas (myenteric ganglion cells) en el rectosigmoide de casos de megacolon congénito probablemente representa una malformación del sistema parasimpatico pelvico.

La resección de la porción del intestino carente de estas celulas nerviosas debe resultar en la curación de estos casos. Se describe una nueva técnica operatoria la cual permite la resección de la parte afectada del recto y rectosigmoide con preservación completa del esfinter anal. Este método ha sido usado en 82 pacientes con resultados clinicos excelentes. Solo dos defunciones, ambas en infantes, han ocurrido en esta serie. Todos los otros niños operados están libre de síntomas. Los primeros pacientes de esta serie fueron operados hace cuatro años. Estudios radiológicos subsequentes de estos casos, reveló que la regresión del colon a su tamaño normal aproximado ocurrió entre los 10 y 12 meses después de la operación.

20 Ash Street

CLINICAL OBSERVATIONS ON TRICHOCEPHALUS TRICHIURUS (WHIPWORM) INFESTATION IN CHILDREN

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TRICHOCEPHALUS TRICHIURUS (whipworm) infestation has been considered by some pediatricians and parasitologists as a relatively benign condition. Others have ascribed to the infestation a number of severe symptoms which could have been due to other concurrent diseases.[1] Few have considered the character and severity of symptoms in relation to worm-burden.

Fernán-Núñez[2] and others[3-5] have reported cases of dysentery due to trichocephaliasis, which were clinically similar to those due to amebiasis. In 1945 Whittier et al.[6] observed in children heavily infected with T. trichiurus a syndrome consisting of diarrhea of from one to three months' duration with stools frequently blood-streaked, abdominal pain, tenesmus and loss of weight. In some cases chronic infestation eventually resulted in prolapse of the rectum. Treatments with tetrachlorethylene and *leche de higuerón* orally and 1:1000 hexylresorcinol by enema were not satisfactory. A subsequent report by Einhorn and Miller[7] confirmed the relationship of heavy Trichocephalus infestation to dysentery and described successful use of *leche de higueron* enema as treatment.

The data to be reported here, based on a study of 352 cases of whipworm infestation among 2000 admissions corroborate the findings that diarrhea, dysentery and prolapse of the rectum may be caused by infestation with whipworm and suggest that the reason for the indefinite status of the parasite as a pathogen has been failure properly to consider the importance of worm-burden relative to the character and severity of symptoms.

METHODS AND MATERIALS

Since 1946 data regarding human whipworn infestations have been recorded by the writers. The great majority of patients studied have been children whose infestations were recognized by fecal examination done as a part of the routine work-up on admission to the hospital. Stools were examined both grossly and microscopically and in the clinically suspicious cases special efforts were put forth to demonstrate the presence of Endamoeba histolytica. During the latter part of the study record was also kept of the presence of Charcot-Leyden crystals. Whether or not direct smear examination revealed parasites, stools were routinely subjected to zinc sulfate centrifugal flotation.

The ova of Trichocephalus in stools from about two-thirds of the patients with whipworm infestation were counted by means of the direct smear method[8] to determine the relative worm-burden. Smears containing 1/300 cc. feces were used and the counts generally were made on oil-cleared dry smears.[9] Estimates by several authors[10-12] of whipworm egg output in terms of eggs/female/cc. feces vary from around 300 downward. On the basis of these reports, it was assumed that counts of 100 eggs/standard smear (30,000/cc. feces) probably represent a worm-burden in the patient of more than 100 females—possibly as many as 1000 mature worms (males and females). In practice, however, the cases were followed by egg-counts without conversion to eggs/cc. or worm-burden.

A multitude of symptoms has been ascribed to Trichocephalus infestation. It was not the intent

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of the present writers to prove or disprove all of them. Since most of the patients had other illnesses in addition to trichocephaliasis, note was made only of symptoms which might have been gastrointestinal in origin, particularly diarrhea, dysentery and visible prolapse of the rectum. Other signs and symptoms noted included abdominal pain and tenderness, nausea, vomiting, distention, constipation, anorexia, bloody nondysenteric stools, physical or mental underdevelopment, and eosinophilia.

Almost all the patients with high Trichocephalus egg-counts or with symptoms suggestive of heavy whipworm infestation were subjected to sigmoidoscopy. It was recognized that in some cases hyperemia, edema or even bleeding of the mucosa were due to the trauma of repeated enemata or to the procedure of sigmoidoscopy itself.

Mature whipworms were readily seen and recognized through the sigmoidoscope as white, somewhat transparent, cylindric organisms firmly attached by having the slender anterior portion of the body threaded into the mucosa. When touched by an instrument they usually contracted into a

TABLE 1

RELATIONSHIP OF WORM-BURDEN TO AGE

Age in Yr.	No. of Cases	Range of Eggs/Smear	Median Eggs/Smear*
<1	0	—	—
1	23	<1–394	12.0
2	47	<1–3277	96.0
3	23	<1–725	28.5
4	26	1–506	13.0
5	18	<1–286	11.0
6	17	<1–116	9.0
7	14	<1–269	8.5
8	14	<1–262	7.5
9	12	1–74	2.0
10	11	2–65	6.0
11	10	<1–42	1.5

* For eggs/cc. stool, multiply by 300.

tight spiral. The embedded slender portion of the worm usually could not be detected. The immature worms are slender and almost transparent and oftentimes are completely obscured by relatively thin films of mucus and debris in the bowel.

At each sigmoidoscopy material for microscopic study was taken by aspiration or swabbing. If lesions were present at least one sample was taken directly from a lesion. The material was examined immediately for Endamoeba histolytica, or other organisms, Charcot-Leyden crystals, pus or blood.

Treatment by commercially available orally administered drugs was found not to be satisfactory for patients with worms in the rectum and sigmoid colon. Such heavily infested individuals were treated following cleansing enemas with an enema containing 0.2 or 0.1% hexylresorcinol in water. Hexylresorcinol is a relatively nontoxic, poorly absorbed drug. Its action on the parasite is a caustic one, destroying the tissues of the worm where they are touched. The mucosa of the bowel, on the other hand, is protected from damage by its coating of mucus, which combines with and neutralizes the drug. In order to prevent burning of the skin by hexylresorcinol in the enema return, vaseline was applied to the perineum, thighs and buttocks. The enema was administered slowly. In all cases, except one adult who was given 750 cc., the total volume of enema fluid was 250 cc. Subsequent to the present study, the quantity of 0.2% emulsion has been increased to 500 to 700 cc. This amount is well tolerated and the results obtained have been consistently good. Retention of the enema for ½ hr. was encouraged. If the return did not take place within 1 hr. a small additional tap-water enema was given to stimulate return.

Whenever possible, patients were sigmoidoscoped again 48 hr. after treatment. Exceptions are entered in the tables which follow. For at least a week after treatment, if possible, and in some instances for much longer periods, patients were observed for changes of symptoms following

TABLE 2

INCIDENCE OF AMEBIASIS AND ASCARIASIS AMONG CASES OF TRICHOCEPHALIASIS OF VARYING SEVERITY

Eggs/Smear	No. of Patients	No. of Asc. Inf.	Per Cent with Ascariasis	No. of E. Hist. Inf.	Per Cent with Amebiasis
0–24	125	58	46.4	4	3.2
25–99	44	22	50.0	5	11.4
100–300	33	20	60.6	5	15.2
300	18	9	50.0	11	61.1
Totals	220	109	49.5	25	11.4

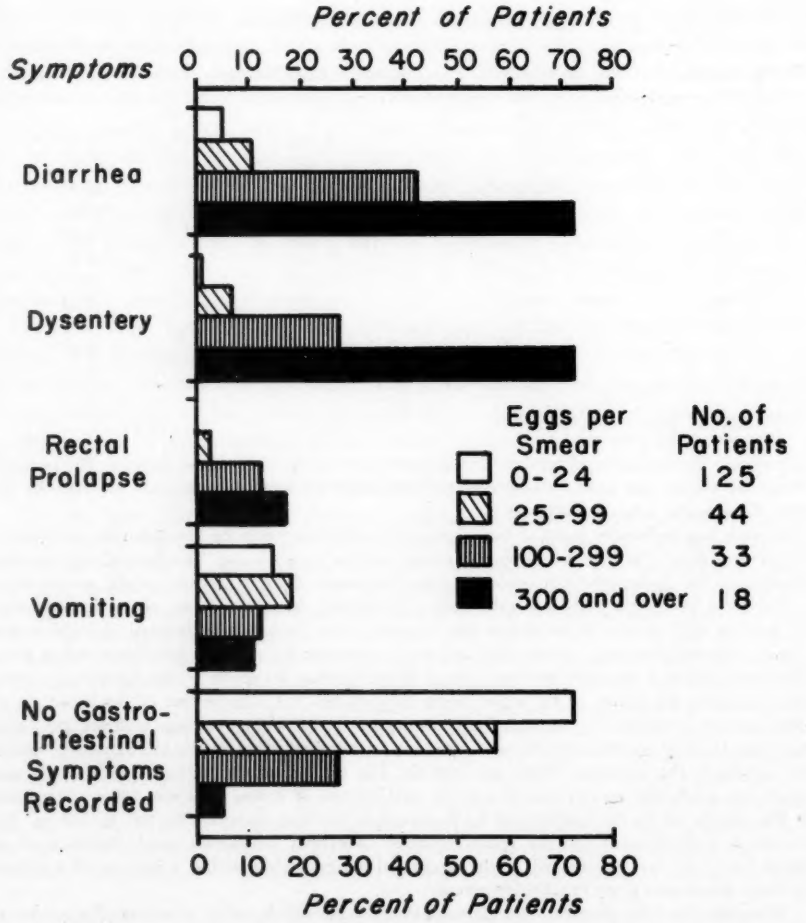

CHART 1. Relation of symptoms to Trichocephalus worm burden Per cent of patients at each level of infestation having specific gastrointestinal symptoms.

FIG. 1. Prolapsed rectum bearing numerous mature Trichocephalus trichiurus. Slightly reduced.

treatment. Because of the destruction of a large proportion of the worms in the bowel, estimation of the reduction in worm burden was obtained by means of follow-up egg-counts rather than by worm-count.

RESULTS

Three hundred fifty-two cases of whipworm infestation were studied. On at least one stool from each of 220 of the patients egg-counts were made. The medians of the initial egg-counts grouped according to age are shown in table 1. The age-group 2 to 4 years had by far the highest counts. There were only four individuals above the age of 9 years with high egg-counts. All four of these patients were severely retarded mentally. These four and an additional mental defective 4 years of age have not been included in table 1.

The incidence of infestation with E. histolytica among all patients studied routinely was 2.6% as compared with 13.1% among those with whipworm infestation. When those with whipworm infestation were grouped according to the level of the initial egg-count, it

FIG. 2. Closer view of prolapsed rectum, bearing numerous mature Trichocephalus trichiurus. Magnified 2 ×.

was found that the incidence of amebiasis increased significantly with the egg-count ($X^2 = 17.4$; $p = .001$). This is shown in table 2. The incidence of ascariasis showed no such increase ($X^2 = 2.2$; $p = .57$).

When the frequencies of various gastrointestinal symptoms are determined among cases of whipworm infestation grouped according to egg-count, it is found that diarrhea, dysentery and rectal prolapse are much more frequent among the heavily infested patients (Chart 1, Figs. 1 and 2). The patients with light infestations, on the other hand, are more likely to present no gastrointestinal symptoms at all. Nausea and vomiting occur equally in all groups. There was found to be a definite positive correlation between egg-count and peripheral eosinophilia. Although this was too low ($r = .436$) for purposes of prediction of the degree of eosinophilia in individual patients, the relationship was highly significant ($p. = .00001$).

Cases may be grouped conveniently into two categories depending on whether the whipworm burden (measured by the egg-count) is high. The group called "heavily-infested" consisted of cases with initial egg-counts equal to or above the arbitrary level of 100/standard smear (30,000/cc. stool). This figure was chosen because it seemed to be about the level at which diarrhea or dysentery occurred.

Light to Moderate Infestation: There were 169 cases with initial egg-counts below 100 eggs/smear. Nine (5.3%) of them were also infected with Endamoeba histolytica. Eosinophilia was not a prominent feature and Charcot-Leyden crystals were infrequently observed in the stools. Only 15 or 8.9% of these 169 patients presented symptoms of diarrhea, dysentery or bloody stools. One of them with dysentery harbored an immature infestation which later produced much higher egg-counts. Three others of the 15 also had amebiasis and two balantidiasis.

Heavy Infection: Of the 51 individuals with egg-counts of 100 or more/smear there were only 14 in which diarrhea, dysentery or bloody stools were not recorded (chart 1). Sixteen of the 37 patients (43.2%) for whom the above symptoms were recorded were also infested with E. histolytica. Amebiasis could not be demonstrated in the remaining 21 in spite of repeated efforts. An additional patient mentioned above may be properly considered in this category. This child was markedly symptomatic with dysentery and rectal prolapse. Although the initial egg-count showed only 85 eggs/smear, the maximum count eventually reached was 322. Immature worms were seen on sigmoidoscopy and were recovered after treatment. This suggests that the patient's infestation matured after the initial egg-count. Several of these patients had marked eosinophilia, and Charcot-Leyden crystals were frequently observed in the stools of heavily infested patients.

Thirty-one of these patients received some kind of hexylresorcinol enema. In two cases in which undiluted S T 37 was the drug used, treatment was unsuccessful. Another received 0.1% and the remainder 0.2% hexylresorcinol. Although in none of these cases was the whipworm infestation eradicated, the treatment was of definite value. Seven cases cannot be used in evaluating treatment either because of absence of symptoms before treatment or of incomplete follow-up after treatment. The effect of treatment directed toward removing worms from the rectum and sigmoid colon in the remaining 24 cases can be better evaluated by considering them in four categories indicated below. Pre-treatment observations and results of treatment are tabulated in tables 3 to 5.

I. Uncomplicated whipworm infestation.

There were 10 patients in this category, all with symptoms of diarrhea, dysentery or rectal prolapse. Treatment with hexylresorcinol enema produced symptomatic cure in 1 to 10 days in eight cases.

TABLE 3

RESULTS OF TREATMENT* OF UNCOMPLICATED TRICHOCEPHALIASIS

Case No.	Pretreatment		Post-treatment	
	Symptoms	Sigmoidoscopy	Days after Treatment Symptom-Free	Sigmoidoscopy
148	Prolapse Dysentery	Bleeding ulcer Worms	1	Normal
174	Prolaps Bloody stools	Pinpoint ulcers Worms	Failure, prolapse continued	Not done
176	Dysentery	No lesions Worms	3	Normal
192	Diarrhea	No lesions Worms	1	Not done
195	Dysentery	No lesions Worms	3	Normal
203	Prolapse Dysentery	Bleeding ulcers Worms	—†	Lesions greatly decreased, no worms
208	Dysentery	Edematous mucosa Worms	10	Not done
215	Dysentery	No lesions Worms	2	Not done
217	Dysentery	Petechial hemorrhage Worms	2	Normal
218	Dysentery	Small ulcers Many worms	3	4 worms seen, otherwise normal

* Treatment with 0.2% hexylresorcinol enema, excepting Case 218, in which 0.1% hexylresorcinol enema was given.

† Follow-up inadequate to judge effect of treatment.

II. Whipworm infestation complicated by amebiasis, the amebiasis being treated first.

There were five dysenteric patients in this category, three with rectal prolapse also. Although anti-amebic treatment in all cases was successful as evidenced by failure of repeated attempts to demonstrate E. histolytica after treatment, diarrhea persisted in three patients. These patients were cured by hexylresorcinol enema.

III. Whipworm infestation complicated by amebiasis, whipworm infestation being treated first.

There were six patients in this category, all with diarrhea or dysentery. Three of the patients became asymptomatic when treated with hexylresorcinol enema in spite of the fact that E. histolytica could still be readily recovered from stools and sigmoidoscopic material. The remaining three symptomatic patients became asymptomatic only after cure of the amebiasis.

IV. Whipworm infestation complicated by amebiasis, both infestations being treated simultaneously. There was but a single case in this category. This patient had dysentery when admitted and was found on sigmoidoscopy to have ulcers and numerous Trichocephalus worms in the rectum and sigmoid. Trophozoites of E. histolytica were in the aspirate. He was given an enema of 0.2% hexylresorcinol and treatment of the amebiasis with aureomycin was simultaneously initiated. Within four days the patient was having normal stools and sigmoidoscopy revealed a normal mucosa.

TABLE 4

RESULTS OF TREATMENT OF TRICHOCEPHALIASIS AND AMEBIASIS, AMEBIASIS BEING TREATED FIRST

Case No.	Amebiasis				Trichocephaliasis	
	Pretreatment		Post-treatment		Post-treatment	
	Symptoms	Sigmoidoscopy	Symptoms	Sigmoidoscopy	Symptoms	Sigmoidoscopy
180	Prolapse Dysentery	E. histolytica Bleeding ulcers Worms	None	No Endamoebae Bleeding ulcers Worms	None	Normal
185	Prolapse Diarrhea Dysentery	Not done	Diarrhea	No amebae Ulcers present Worms	None	Normal
193	Dysentery	E. histolytica Bleeding ulcers Worms	None	No Endamoebae Hemorrhagic ulcers Worms	None	Slight hyperemia, 2 worms present
201	Dysentery	E. histolytica Bleeding ulcers Worms	Diarrhea	No Endamoebae Bowel hyperemia Worms	None*	Normal
201	Prolapse Dysentery	E. histolytica Bleeding ulcers Worms	Diarrhea	No Endamoebae Ulcers fewer Worms	None	Normal

* Required 3 treatments; symptoms did not decrease, nor did hyperemia and edema of bowel subside until worms were removed by third treatment.

CASE REPORT

Case 210. J. H., a Negro male 3 yr. of age, was admitted with a chief complaint of dysentery. Four months previously the child had begun to have frequent watery stools, reaching a peak of 15 to 25 daily in mid-July. Blood and mucus became evident in the stools in July. About 1 wk. before admission edema of the face and feet were noted. Treatment for worms was given by a local physician who recommended hospitalization because of severe anemia. System review was negative except for history of dirt-eating and tardiness in learning to talk.

On admission he was found to have: temperature, 37.8° C. (rectal); pulse, 148/min.; blood pressure, 100/50 mm. Hg. The child appeared well-developed but chronically ill. There was pitting edema of the ankles and sacral region. Nail-beds, lips, mucous membranes and conjunctivae were pale. The lungs were clear. The heart was normal except for a grade III systolic murmur loudest at the apex but heard in all valve areas. The sharp edge of the liver could be felt 2 cm. below the costal margin at the midclavicular line. Rectal examination was negative.

Laboratory studies revealed the patient to have a moderately severe hypochromic anemia and an eosinophilia amounting to 24% of 9,350 cells/cmm. Blood and cultures of stools were negative for pathogens. Blood was found to be present in the stool by means of the benzidine test. There were approximately 600 Ascaris and 300 Trichocephalus eggs/smear.

Initial sigmoidoscopy on the third hospital day revealed that the rectum and sigmoid colon were lined with T. trichiurus. Many punctate hemorrhagic areas were in the mucosa. Material obtained by swabbing contained many motile trophozoites of E. histolytica.

During the first week of hospitalization the patient received a total of 440 cc. whole blood which brought the Hgb. level up to 10.5 gm./100 cc. Although there had been no history of rectal pro-

TABLE 5

RESULTS OF TREATMENT OF TRICHOCEPHALIASIS AND AMEBIASIS, TRICHOCEPHALIASIS BEING TREATED FIRST

Case No.	Trichocephaliasis				Amebiasis	
	Pretreatment		Post-treatment		Post-treatment	
	Symptoms	Sigmoidoscopy	Symptoms	Sigmoidoscopy	Symptoms	Sigmoidoscopy
205	Dysentery	E. histolytica Bleeding ulcers Worms	None	Normal	None	Not done
206	Dysentery	E. histolytica No lesions Worms	None	Not done	None	Not done
209	Dysentery	E. histolytica Ulcers Worms	Diarrhea	E. histolytica Ulcers fewer No worms	None	Ulcers almost all healed
211	Diarrhea	E. histolytica No ulcers Worms	Diarrhea	E. histolytica Bowel normal	None	Normal
213	Diarrhea	No E. histolytica Ulcers present Worms	Diarrhea	Not done	None	Normal
214	Dysentery	No Endamoebae Ulcers Worms	None	E. histolytica Ulcers Worms absent	None	Not done

lapse, this was observed following administration of enemas in preparation for sigmoidoscopy. Worms were observed to be attached to the angry red mucosca of the prolapsed rectum. Figures 1 and 2 illustrate this condition in a similar case.

Oral aureomycin 250 mg. every 8 hr. was begun on the seventh day and continued 5 days as treatment for amebiasis. The appearance of the rectal mucosa on sigmoidoscopy on the second day of treatment was improved but there were still ulcers and diffuse inflammation of the mucosa. Amebae were not observed at this time and never reappeared either in stools or sigmoidoscopic material during the patient's hospitalization, but stools continued to be bloody, mucoid and frequent. Curing the patient's Ascaris infection by two 0.6 gm. doses of hexylresorcinol tablets on the 15th and 21st days of hospitalization produced no improvement in the character of the stools.

A month after admission the patient received a retention enema of 0.2% hexylresorcinol. Two days later sigmoidoscopy revealed normal mucosa with no worms. Stools became normal in character and frequency within 5 days. Egg-counts indicated that about 75% of the mature worms had been removed, and the patient was discharged in good condition 2 mo. after admission.

DISCUSSION

It is apparent that heavy infestation with the whipworm may result in diarrhea or dysentery frequently eventuating in prolapse of the rectum. The correlation of trichocephaliasis and amebiasis has been shown to point out a pitfall of differential diagnosis of dysentery, that of attributing dysentery solely to amebiasis, simply because Endamoeba

histolytica is present in the stools. The frequency of dysentery among cases of trichocephaliasis without amebiasis and the symptomatic improvement of cases with or without amebiasis when treated for the helminthic infestation indicate that Trichocephalus trichiurus may be at least as important an agent as Endamoeba histolytica when both are present.

To explain the apparently greatly increased incidence of amebiasis among the cases of heavy whipworm infestation poses a fascinating problem. It may result from one or more of several factors. The correlation may be due in part to the fact that both are the result of a similarly contaminated environment. The damage to the bowel produced by the heavy trichocephaliasis may predispose to amebic infestation. Again, there may be an increased susceptibility to both parasites because of nutritional or constitutional factors. Finally, the correlation may not be real but merely apparent, reflecting the greater ease of diagnosing amebiasis in a diarrheic patient (the diarrhea here being caused by the helminth), the copious mucus characteristic of heavy whipworm infestations serving admirably to preserve trophozoites of Endamoeba histolytica in a readily recognizable condition.

Treatment of uncomplicated trichocephaliasis by hexylresorcinol enema was successful in all but one case when 0.2% suspension was used; results with 0.1% or ST 37 used in three cases were not as favorable. A commercially available 0.2% hexylresorcinol solution or suspension would seem desirable. The results obtained when trichocephaliasis is complicated by amebiasis show that symptoms may be primarily due to either infestation or partly to both. There is no evident contradiction to simultaneous treatment of both infestations.

Summary

Of about 2000 hospitalized children whose stools were examined routinely, 18% were infested with Trichocephalus trichiurus. The heavy infestations (over 30,000 eggs/cc.), which consistently produced diarrhea and dysentery, were most common in children 2 to 4 years of age. A significant correlation existed between worm-burden and incidence of amebiasis.

A successful technic for the treatment of trichocephaliasis is described. The importance to the clinician of measuring worm burden is emphasized.

Addendum

After this report was submitted for publication, it came to the writers' attention that Basnuevo[13,14] recently reported successful treatment of trichocephaliasis, using essentially the procedures developed by this study.

Acknowledgment

Grateful acknowledgment is made to Dr. R. V. Platou of the Tulane Department of Pediatrics and to the many residents and interns of Charity Hospital who assisted in this work; also to Drs. W. A. Feier and J. W. Crosson of Sharp & Dohme, Inc., for technical advice and assistance.

References

1. Swartzwelder, J. C., *Trichocephalus trichiurus* infection: Analysis of eighty-one cases, Am. J. Trop. Med. **19**:473, 1939.
2. Fernán-Núñez, M., Pathogenic role of *Trichocephalus dispar* (Trichuris trichiura), Arch. Int. Med. **40**:46, 1927.

3. Ross, F., Chronic diarrhea due to *Trichocephalus trichiurus,* Lancet **2**:97, 1942.
4. Pallister, R. A., Trichiuriasis in Malaya, Malayan M. J. **8**:303, 1933.
5. Plessen, M., *Trichocephalus dispar,* um parasita patogenico, An. Inst. med. trop. **2**:247, 1945.
6. Whittier, L., Einhorn, N. H., and Miller, J. F., Trichiuriasis in children: Clinical survey of fifty cases and reports of three cases with heavy infection and striking clinical symptoms, Am. J. Dis. Child. **70**:289, 1945.
7. Einhorn, N. H., and Miller, J. F., Intestinal helminthiases: Clinical survey of six hundred and eighteen cases of infection with common intestinal helminths in children, Am. J. Trop. Med. **26**:497, 1946.
8. Beaver, P., Quantitative hookworm diagnosis by direct smear, J. Parasitol. **35**:125, 1949.
9. Beaver, P., Standardization of fecal smears for estimating egg production and worm burden, J. Parasitol. **36**:451, 1950.
10. Alvares Corrêa, M., and Melloné, O., Estudo sobre a postura do *Trichuris trichiura,* A Folha Medica **19**:137, 1938.
11. Burrows, R. B., On estimation of *Trichuris* worm burdens in patients, J. Parasitol. **36**:227, 1950.
12. Manalang, C., Trichuriasis: Relation between number of ova per gram of formed stool and number of female worms harbored by host, Philippine J. Sc. **35**:11, 1928.
13. Basnuevo, J., Hexilresorcinol en forma liquida para enemas e instilation duodenal, Rev. Kuba **5**:119, 1949.
14. Basnuevo, J., El Hexilresorcinol en el tratamiento de la tricocefaliasis rectal, Rev. Kuba **7**:17, 1951.

SPANISH ABSTRACT

Observaciones Clínicas en la Tricocefaliasis del Niño

El 17.6% de más de 1900 niños hospitalizados cuyas heces fecales fueron examinadas, demostraron infección con Trichocephalus trichiuris. La tara de Trichocephalus se calculó en 220 pacientes por el método del extendido fecal directo. Infecciones severas (más de 30,000 ovas por cc.), las cuales consistentemente produjeron diarrea y disentería y a veces prolapso rectal, fueron más communes en niños entre las edades de 2 a 4 años. Estos síntomas eran raros en infecciones leves. Hubo correlación estatísticamente significativa entre la tara de Trichocephalus y la incidencia de amebiasis. Tratamiento con enema de retención de solución acuosa de hexylresorcinol al 0.2% produjo mejorías sintomáticas, aunque las infecciones no fueron eradicadas.

Tulane University of Louisiana School of Medicine

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

Round Table Discussion

IMMUNIZATION REVIEW

AIMS C. MCGUINNESS, M.D., *Chairman,* Philadelphia
E. O. JODAR, M.D., Detroit, and JOHN FLEEK MILLER, M.D., Newark, Ohio, *Secretaries*

Chairman McGuinness: Ladies and gentlemen: it is presumptuous for one person to stand here and discuss alone immunization against a dozen diseases. Many of you know much more concerning many phases of the subject than your chairman. I therefore ask you all to help by free discussion in making this a round table in the true sense.

DIPHTHERIA, TETANUS AND WHOOPING COUGH

I shall talk first about diphtheria, tetanus and whooping cough, and the use of single and then multiple antigens. Following this we will have a short period for discussion.

Diphtheria: Up to World War II it was generally assumed that most of the adult population of the United States was immune to diphtheria. Many studies since 1941 have shown this is no longer the case. Depending upon locality 25 to 50% of our adult population now is susceptible. Infants of susceptible mothers likewise are not immune, and there has been an increasing amount of diphtheria in infants under 6 months of age. This phenomenon, of course, is due to the steadily decreasing carrier rates. Immunity to diphtheria depends upon constant restimulation which now, in general, must be provided artificially. Immunity following active immunization cannot be counted on lasting more than 3 to 4 years.

Reactions to diphtheria toxoid have been one of the chief problems in diphtheria immunization, especially in older children and adults. Methods of purification developed by Pillemer and others in recent years have made available vastly superior toxoids which also contain considerably less alum than the pre-War products. One must remember, however, that some individuals are sensitive to toxoid itself, and such persons will react adversely to the material regardless of its freedom from impurities. Most infants and young children are not sensitive to diphtheria toxoid. Older children and adults should receive a Schick test and Schick test control prior to immunization in order to rule out those who definitely are sensitive to the material. Injections should be given deep subcutaneously or intramuscularly, otherwise the normally occurring allergenic cyst may break through the surface and result in a draining "abscess." Alum toxoids, either alum-precipitated or aluminum hydroxide-adsorbed, are far more antigenic than fluid toxoids, probably cause no more reaction, and therefore are

From the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 17, 1950.

the materials of choice. With respect to dosage, package instructions should be followed. In general, one immunizing dose is incorporated in 0.5 cc. of material. Two doses should be given at approximately one month intervals followed by a third dose 6 to 12 months later. Primary immunization should not be considered complete until the third dose has been given. If fluid toxoid is used 3 injections should be given in the initial series instead of 2. Schick testing is recommended prior to active immunization of older children and adults. If this is not possible the first dose should be 0.1 cc. of toxoid. Individuals reacting adversely to 0.1 cc. of toxoid should be given no further injections. If no reaction occurs following injection of 0.1 cc. of toxoid it probably is safe to proceed with 2 injections of 0.3 to 0.5 cc. each. Once an individual has received the basic series of injections (3 doses), 0.1 cc. of toxoid given every 3 to 4 years will maintain an adequate level of immunity. While I will discuss the problem later, there is ample evidence for starting diphtheria immunization early, say at about 2 months of age.

Pertussis: As 60% of the deaths from whooping cough occur in infants under 6 months of age, it obviously is desirable to immunize as early in life as feasible. Ample evidence is now available to show that most young infants do develop good antibody levels, particularly when the vaccine is mixed with alum or alum toxoids. It is recommended that there be intervals of 3 to 4 weeks between injections, Dr. Sauer being of the opinion the duration of immunity is longer than when injections are given at shorter intervals. Rapid protective levels can be attained by giving the vaccine at shorter intervals (one week) and one week intervals are recommended when pertussis is epidemic in a community. The matter of duration of immunity can be dealt with by giving booster injections. For many years there has been difference of opinion as to the relative merits of vaccines grown on medium containing human blood versus medium containing sheep blood. This argument has been settled by a recent ruling of the National Institute of Health which prohibits the use of human blood because of the potential danger of transmitting serum hepatitis. Selection of strains for antigenicity probably is the most important factor in vaccine production today. Dr. Emmett Holt, Jr., and his associates have been using unkilled organisms without adverse reaction and preliminary results indicate such vaccines may be much more antigenic than vaccines containing killed organisms. Of importance is the fact that some individuals inherently are unable to produce good antibody levels regardless of the amount of antigen injected. Dr. Pearl Kendrick and associates have shown a relatively high degree of immunity persists for about 4 years following active immunization against pertussis. On the basis of these studies, booster injections are recommended every 3 to 4 years. Previously immunized children should be given a single injection (15 to 20 billion organisms) following known exposure. Children not previously immunized should following exposure be given hyperimmune serum; preferably human serum in the lyophilized form or its gamma globulin fraction. Reactions to pertussis vaccine, particularly those of the encephalitic type, have been the cause of considerable concern. Infants with histories of convulsions and children with respiratory infections or in active stages of teething should not be immunized. A febrile reaction following an injection of pertussis vaccine should be cause for considerable caution in determining whether further injections should be given, and the amount of antigen injected. If there is any question it is better to err on the side of conservatism.

Tetanus: Tetanus toxoid is one of the best antigens available, and the youngest infants respond well with minimal reaction. Its effectiveness has been demonstrated beyond any doubt, and I feel every individual should be immunized against the hazard of this disease. Tetanus toxoids have been purified in the same manner as diphtheria toxoid. The alum-precipitated and aluminum hydroxide-adsorbed materials are antigenically superior to the fluid toxoids, and are recommended especially for primary immunization. Fluid toxoids give a slightly more rapid booster response. For primary immunization 0.5 cc. of toxoid should be injected twice at approximately one month intervals, 3 doses being necessary if fluid toxoid is used. Booster doses (0.5 cc.) should routinely be given at 3 year intervals. If an injury occurs when 4 years or more have elapsed since a booster dose, antitoxin (3000 units) should be given in addition to toxoid on the basis of the important studies of Dr. John Miller and his associates. In certain instances of massive wounding it may be advisable to give antitoxin as well as toxoid regardless of the time elapsed since the last booster, as the incubation period of tetanus in such cases occasionally may be as short as 24 hours.

Multiple Antigens: The value of the multiple antigens, particularly those containing diphtheria and tetanus toxoids with pertussis vaccine, is established beyond doubt. In addition to reducing the number of injections required for active immunization of infants, there is evidence resulting antibody

levels are superior to those obtained from injection of single antigens. Reactions in infants and young children are no more severe following injection of triple antigens than following injection of single antigens. Children over 4 years of age do appear to react more severely to the multiple antigens, however, and single antigens are recommended in children beyond that age. The antibody response is good in most infants after 2 months of age. Infants possessing maternal antibody against diphtheria may not respond as well to the initial series of injections, but they are temporarily immune anyhow, and will achieve good levels following injection of the first booster dose. The schedule recommended is three 0.5 cc. injections at monthly intervals starting at 2 to 3 months of age; a fourth dose at 12 to 18 months of age; and a booster dose at 3 to 4 years of age. This schedule will provide protection against diphtheria, tetanus and whooping cough from early infancy until school age.

Discussion

Question: Should I give pertussis vaccine to a child with a history of convulsions?

Chairman McGuinness: As suggested before, a history of convulsive seizures should make one hesitant about attempting active immunization against pertussis. If a decision is reached to attempt immunization the initial dose of vaccine should be small, say 0.1 cc. saline vaccine. Subsequent doses should be increased cautiously on the basis of tolerance of preceding doses.

Question: Does this warning concerning convulsions apply equally to tetanus and diphtheria as it does to whooping cough?

Chairman McGuinness: No.

Dr. M. W. Seymour, Columbus, Ohio: Would you say something about the formation of subcutaneous nodules?

Chairman McGuinness: Nodules, or "allergenic cysts," as they sometimes are called, are a normal reaction to the local irritation set up by the antigen. In some individuals these cysts are larger than in others. Following injection of some of the older antigens, especially those containing large amounts of alum, these cystic reactions were larger and frequently drained through the skin surface. This is far less likely to occur following injection of the newer improved antigens; nonetheless, it is advisable to inject antigens deep subcutaneously or even intramuscularly.

Question: When a child who is not actively immunized against tetanus is given antitoxin following an injury, how soon after that antitoxin injection can you start active immunization?

Chairman McGuinness: Active immunization may be started immediately as long as the toxoid is not injected at the same site (or in the same syringe) as the antitoxin.

Question: What is the best site for injection of antigens?

Chairman McGuinness: I prefer the arm. Some individuals like to inject into the buttock, although I feel there is, at least theoretically, a greater chance for infection from injections given in the diaper area.

Question: What about the question of there being a possible relationship between poliomyelitis and antigen injections?

Chairman McGuinness: There have been recent reports by McClockey, Hill and MacCallum indicating that in Australia and in England there has been found evidence that when poliomyelitis has been preceded within several weeks by an antigen injection, paralysis has tended to be localized in the extremity where the injection was given. There is apparently no evidence to suggest that the antigen injections have increased susceptibility to poliomyelitis. I have seen no reports indicating that this phenomenon has been observed in the United States but I do know that in view of the British and Australian reports the National Foundation for Infantile Paralysis has the matter under extensive study in a number of areas.

Dr. Nelles Silverthorne, Toronto, Canada: To our knowledge, in the Dominion of Canada, and to those also in the United States who have had experience with an epidemic of poliomyelitis, and with all the inoculations which have been given, it would be a strange thing if one physician somewhere hadn't noticed the relationship before now. Certainly we have had no incidence in Canada. I am afraid we are a little old-fashioned concerning the use of alum-precipitated toxoids. We still use the fluid toxoid prepared by the Connaught Medical Research Laboratories for the following reasons: we have had no paralysis, and to my knowledge no outbreaks of whooping cough in private practice in those who have received booster doses. In my own experience in children up to 4 to 5 years of age, and up to 10, I have never seen a serious reaction on a booster dose at an age comparable to which you have been discussing.

Now one question: Is agglutination the only index of pertussis immunity?

Chairman McGuinness: No, I am sure it is not. It is a relatively simple test, however, and seems to correlate fairly well with actual clinical experience. With respect to encephalopathies following pertussis vaccine, many of the cases reported followed injection of saline (not alum) vaccine.

Typhoid, Scarlet Fever and Smallpox

I shall speak but briefly concerning active immunization against these 3 diseases.

Typhoid immunization in children is generally limited to special situations or in particular parts of the country where the disease is endemic. One fourth to one half the adult dose of triple vaccine is recommended, depending upon the age of the child.

Scarlet fever immunization is recommended only for professional personnel—physicians and nurses—who are Dick test-positive and must work in communicable disease hospitals.

With regard to smallpox vaccination I should like to emphasize that the present calf lymph vaccines are very labile and deteriorate rapidly when not properly refrigerated. They also deteriorate with age. It is important to know that nonimmune individuals may develop a lesion with the appearance of an immune reaction following vaccination with deteriorated material. In any batch of vaccine points one should get a sufficient number of typical "takes" to establish the fact the material is of good potency.

Vaccination is recommended during the first year of life and should be repeated at 3 to 4 year intervals thereafter. Vaccination always should be carried out in the face of a possible contact or threatened epidemic.

Discussion

Dr. James B. Stewart, East Cleveland, Ohio: What about intradermal vaccination?

Chairman McGuinness: Intradermal vaccination has been carried out using egg fluid vaccines. The immunity following vaccination with egg fluid materials has not proved to be as satisfactory as that obtained with calf lymph vaccine. I would not recommend the intradermal injection of calf lymph vaccine, as sufficient virus is introduced by the multiple pressure method, and severe reactions might follow the amount of virus one would introduce by intradermal injection.

Dr. Hoyne, when you fail to get a "take" following smallpox vaccination, how many further attempts do you make, and at what intervals?

Dr. Archibald L. Hoyne, Chicago: I believe that everyone who has not had smallpox should obtain at least one successful vaccination in a lifetime. Ordinarily, if there were no reaction I would repeat the vaccination yearly. In case of known exposure to smallpox, I would vaccinate every third day until there was some local evidence to reaction.

Rocky Mountain Spotted Fever

Chairman McGuinness: Vaccination is recommended only for those in or going into definitely endemic areas. The newer antibiotics are so effective in the treatment of this disease there seems to be little justification in the vaccination as it used to be carried out in any area where there were ticks.

Measles

The effectiveness of gamma globulin (immune serum globulin—human) in measles prophylaxis is established beyond doubt and is recommended following known exposure of susceptibles. Excepting under unusual circumstances, one should attempt to modify rather than afford complete protection.

German Measles

Children should be permitted, in fact encouraged, to get german measles. Because of the hazard to the young fetus we need some means of protecting women who become exposed to this disease during the first trimester of pregnancy. Convalescent serum has not given satisfactory results, and there is considerable question as to the usefulness of gamma globulin (immune serum globulin—human). Until more definite information is available, however, I would recommend two 6 to 8 cc. doses of gamma globulin at 5 to 7 day intervals for women exposed to the disease in early pregnancy. I believe that equally important is the removal of the pregnant women from the source of infection at the earliest possible moment.

Influenza

Vaccination against influenza is not recommended for children excepting under special circumstances; e.g., a child with rheumatic fever in whom even a mild case of influenza would be considered hazardous.

Mumps—Active Immunization

Active immunization against mumps is indicated infrequently in children. The vaccine promises to be very useful for immunizing susceptible adults, although to date it would appear the immunity resulting from injection of mumps vaccine is relatively short—perhaps 6 months to a year. If following active immunization an individual is exposed frequently to the disease his immunity could be expected to be enhanced and prolonged through inapparent infection.

A useful adjunct in the field of mumps is the skin test for susceptibility which gives a positive tuberculin-like reaction in immune individuals. It is suggested that adults be skin-tested prior to being given vaccine as so many adults already are immune by virtue of previous inapparent infection.

Mumps—Passive Immunization and Treatment

Early results from use of convalescent serum in both passive immunization and treatment are inconclusive, except that in one well-controlled study in which the equivalent of 200 cc. convalescent serum was used in treatment, the incidence of orchitis in the treated group was 7% as compared with 28% in the controls. Serum from vaccinated donors (hyperimmune serum) is now under study in Philadelphia and preliminary results indicate this material may be of use both in passive immunization and treatment. Large doses of serum are necessary—50 cc. for passive immunization of exposed susceptibles and 200 cc. for treatment. Passive immunization and treatment generally are reserved for adult males.

Whooping Cough—Passive Immunization and Treatment

Hyperimmune serum, either in vacuum-dried form or in the form of its gamma globulin fraction, has been found useful both in passive immunization of exposed susceptibles and in treatment of the disease. The vacuum-dried form has the advantage of being safe for intravenous injection which is not the case with the gamma globulin fraction. There is evidence the newer antibiotics may be of some benefit in treatment, but it is felt that when the disease occurs in small infants the serum always should be given in addition to the antibiotics when the latter can be tolerated. Hyperimmune rabbit serum also is probably of some value, but the human products (which now are irradiated as a precaution against serum hepatitis) are to be preferred.

Pediatrics

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous"

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

PAEDIATRIC EDUCATION IN CANADA

IN COMMON with most medical schools on this Continent at the beginning of the present century, the subject of paediatrics was a very minor one and often nonexistent in the medical curriculum of Canadian medical schools. With the increasing influence of the European and American developments, pioneer work in Canada in the field of children's medicine and surgery was carried forward until lectures were given to final year medical students, and through a gradual process of demonstration and obvious need the courses have been enlarged until they now embrace subject matter which is generally used in most paediatric departments. Canadian medical schools have gradually developed independent departments of paediatrics and today only one department is still within Internal Medicine. Canadian paediatric departments and children's hospitals have kept pace with developments in the United States, Great Britain and Europe, by a constant interchange of graduate and postgraduate students. This commenced in centres in Germany and Europe and extended to Great Britain and the United States.

In the early days of paediatrics as a specialty in Canada a small group of physicians engaged in teaching as well as practice formed the Canadian Society for the Study of Diseases of Children. They met annually for the presentation of scientific papers and for interchange of ideas. This Society gradually grew until it embraced most of the Certified paediatricians in Canada and assumed the responsibilities of organized paediatrics. It has been responsible through its committees for advising the Royal College of Physicians and Surgeons of Canada regarding requirements for examinations and also standards of paediatric hospitals approved for residencies. At its most recent meeting the Society changed its name and is now known as the Canadian Paediatric Society. Canadian paediatricians have also enjoyed the privilege of becoming Fellows of the American Academy of Pedi-

atrics and a number have belonged to the American Pediatric Society and the American Society for Pediatric Research.

The establishment of the Royal College of Physicians of Canada 21 years ago and subsequently its recognition of specialists in the field of paediatrics added great impetus to standard requirements for the specialty. The Royal College admission requirements for examination are similar to those enforced by the American Board of Pediatrics, and specialist examinations are conducted annually. Generally speaking paediatric departments and hospitals recognised either by the Royal College of Physicians of Canada or the American Board of Pediatrics are reciprocally recognised in each country. In addition to Certification in the specialty of paediatrics the Royal College of Physicians of Canada grants a Fellowship in medicine with emphasis on the subject of paediatrics. Thus a candidate is allowed to proceed to the examination when he has obtained five years of postgraduate training, including general rotation, two years of approved clinical training in a recognised paediatric hospital, and two further years of specialised study or research, one of these years to be in further study of internal medicine. The examination is then conducted in both internal medicine and paediatrics. The standard set for granting the F.R.C.P. to successful candidates in this examination is very high. Such a qualification is being recognised in making appointments to the teaching staff of paediatric departments and hospitals in Canada.

Following the last war there was the universal problem of the increased demand for postgraduate training in paediatrics and Canadian hospitals were flooded with applications for such posts. As a result a larger number than usual of paediatricians have been trained and are settled in various parts of Canada.

In 1947 a survey of Canadian medical schools and paediatric hospitals was conducted in cooperation with the American Academy of Pediatrics. At that time there were nine medical schools and 16 hospitals attached to paediatric departments. Thirty hospitals were visited and surveyed.

The findings of the survey were similar to those in American medical schools and hospitals. However, Canadian paediatrics and medical education have a few conditions which make it somewhat different. One of these is the geographic location across a country which is sparsely settled with the exception of some areas along its southern portion.

In the eastern provinces there is one medical school, the University of Dalhousie at Halifax, Nova Scotia. In Quebec there are two French-speaking medical schools, Laval University at Quebec City where paediatric teaching is conducted in three institutions for children, and the University of Montreal where paediatric teaching is carried on in one of the oldest and largest children's hospitals on the North American continent. McGill University medical school is also located in the city of Montreal and draws its medical students from Canada, the United States and beyond. Its paediatric department embraces the Children's Memorial Hospital and services at the Royal Victoria Hospital.

A new medical school has been established at the University of Ottawa, the capital city of Canada, and its paediatric teaching is conducted mainly at the General Hospital, Ottawa. Queen's University at Kingston, Ontario, on Lake Ontario, divides its paediatric teaching between the General Hospital at Kingston and the Civic Hospital at Ottawa.

At the University of Toronto, which is a provincial university, the teaching of paediatrics is centered chiefly in the Hospital for Sick Children which is the largest children's institution in Canada. At London, Ontario, the University of Western Ontario medical

school carries on its paediatric programme in the War Memorial Children's Hospital, the Victoria General Hospital and St. Joseph's Hospital.

The University of Manitoba at Winnipeg has the facilities of the Children's Hospital and the Grace Hospital. The University of Saskatchewan at Saskatoon offers a premedical course. The students proceed to other medical schools for their clinical years. The University of Alberta carries on its paediatric teaching programme at the University Hospital, Edmonton, and the Alexandra Hospital in the same city.

A new medical school has now been organized at the University of British Columbia in the city of Vancouver. With the addition of new beds at the Vancouver General Hospital and the paediatric services of St. Paul's Hospital and the Children's Hospital the facilities are excellent.

In addition to the university centres there are also well organized paediatric services in the cities of Calgary, Regina, Hamilton, Ontario, and new departments are being added to many of the larger General Hospitals throughout the country.

It will be obvious to any one who is aware of the constant interchange of residents and paediatric visitors from one country to the other that Canadian paediatrics is fashioned very much after the pattern of that in the United States with the additional flavour of the French-speaking schools and the close link which Canada has with our British colleagues.

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DEAR DR. HARPER:

The statement from the American Board of Pediatrics published in your section in the March issue of PEDIATRICS prompted me to send you this account of our seminar on growth and development. It has received a high rating by the residents, the reason probably being that it evolved naturally to meet a desire for more information. For several years, the new residents and internes have been given a briefing on the questions mothers ask in the well baby clinic. Two years ago the residents in child guidance asked for permission to join the group for this briefing. Out of this grew a continuation of the discussion of the child. The group meets every Thursday from 4 to 5 p.m. after the well baby conference. At the beginning of the resident year, July 1, discussion begins on the newborn, and includes rooming-in, prenatal care and instruction, physical characteristics of the newborn, breast feeding, anomalies, informing parents about abnormalities, etc. As many sessions are spent on one age level as questions demand. There is no definite budgeting of time. A period at the beginning of the hour is used to answer questions that may have arisen in the well baby conference immediately preceding. If a problem arises that is not satisfactorily answered by those present, a guest authority in the field is invited for the following week. This may be an obstetrician, a dentist, an anesthetist or an anthropologist.

During the year we have covered the different age periods in this same manner. Growth grids have been discussed, various tables used for nutrition evaluation have been reviewed, etc. At one time we contrasted Spock's book with Holt's! The pros and cons of a nursery school have been discussed by teachers in that field. Education has been presented from the point of view of public and private schools. School health has been reviewed. The

time out of school has been surveyed and we have had the participation of recreational workers and religious instructors. We have asked a mother to answer questions for us and invited teen agers to tell us about their views on education, religion, and recreation.

The growth changes and variations during adolescence have been presented by a guest authority in that field. Juvenile delinquency has been discussed by probation officers and psychiatrists. Films such as Gesell's have been shown.

The Social Service Department has arranged field trips to different children's institutions.

It has seemed to the senior physicians participating that this method of studying the life of the child and the impact of the environment on him should be a part of every pediatrician's and psychiatrist's experience. It circumvents the boredom usually associated with counting teeth and epiphyses. One hour a week during a resident's year does not usurp his time from the care of the acutely ill.

HULDA E. THELANDER, M.D.
University of California
San Francisco

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

REPORT FROM THE A.P.H.A. COMMITTEE ON CHILD HEALTH: A STUDY OF CHILD HEALTH SUPERVISION

AT ABOUT the time the Academy's Study of Child Health Services was completed and many agencies were directing their energies with renewed vigor to the cause of better health for children, the American Public Health Association established a Committee on Child Health. This Committee, organized in 1948 under the chairmanship of Dr. Leona Baumgartner, undertook to coordinate the interests and activities of the various sections of the Association in regard to work with children. The Committee includes representatives from such sections as Maternal and Child Health, Nursing and Nutrition; a considerable proportion of its members are also members of the Academy. Its first project, as described below by its present chairman, Dr. Samuel M. Wishik, has been a study of child health supervision.

* * *

"The Committee on Child Health has undertaken the ambitious task of developing or encouraging the development of statements on recommended practices and guides for the organization and operation of public health programs for children. The first specific task that the committee has tackled is the child health conference. A study staff appointed by the committee reviewed the literature on the subject over the past twenty years, analyzed manuals on the child health conference from health departments of 23 states and 8 cities and reviewed 37 manuals on public health nursing. The material studied has been summarized in a compendium of current practices in this country. With this as a point of reference, the members of the Committee on Child Health are at present in the process of developing a statement on recommended practices.

"The age group covered by child health conferences is usually from birth to school age. While the first year of life is given greatest emphasis, there exists a trend in the direction of taking positive steps to keep the preschool children under health supervision. In the past, parents discontinued seeing the physician when the child reached one year because by that time all the immunizations were completed and special feeding instructions no longer seemed necessary. The same two factors, immunization and feeding, are now instrumental in the continuing supervision of the preschool child. In respect to immunization, booster doses are being given between the first year and school attendance; in respect to feeding, the psychological aspects are of interest to the parent beyond infancy.

"Immunizations against diphtheria and smallpox are routine in all areas. Most areas have also added pertussis immunization and there is a strong trend to the addition of tetanus as well, particularly with the use of combined materials. The universal addition of tetanus whenever diphtheria toxoid is given would be a significant contribution to preventive child health work. Primary immunizations are being given at an earlier age than in former years. Most recently, the desire to avoid immunizing during the poliomyelitis

season has altered the schedules so that a greater attempt is being made to complete the procedures before the summer months or before the infant reaches 6 months of age.

"Feeding probably still rates number one in frequency among child rearing problems but seems to be lessening as a somewhat more permissive atmosphere is being created around the feeding situation. Sleeping problems are probably running a closer second to eating difficulties than was formerly the case.

"The mental health or psychological aspects of child rearing are taking on increasing importance in the work of the child health conference, as in general pediatric thinking and practice today. The primary objective expressed by the majority of child health conferences is to help parents to rear children so that the children will be healthy and the family setting will be a wholesome one. Discussion on feeding, sleeping, habits, discipline and behavior take a prominent place in the work of the child health conference.

"At the same time, distinction is quite clear between these activities and those of a psychiatric service such as a child guidance clinic. The staff members of the child health conference are not expected to be psychiatrists. Their work is focused at the normal range of parental difficulties. Mothers who visit the child health conference can be roughly divided into three groups. First are those who merely need information on child rearing; second are those who have already encountered a difficulty, but one which lends itself to rather easy analysis and solution; third are the mothers whose relationships with their children are so disturbed as to warrant more specialized attention.

"For situations falling into the third of these categories, the child health conference staff must learn the occasion for and method of effective referral. The more simple problems of the second group are now being handled in many child health conferences. It is the first group, however, those who have not yet experienced difficulty, to whom child health conferences are trying to give greatest attention. The terms 'anticipatory guidance' or 'anticipatory counseling' are being used to describe the practice of forewarning mothers of the critical points in child rearing at which troubles commonly begin. When a mother happily reports that her ten month old infant eats a large bowl of cereal, she is told that when the baby will be about 15 months old, he may actually eat less food than now. He will be bigger, but he will be growing less rapidly and need less food. So many feeding difficulties begin because of the mother's concern at the unexpected drop in intake. Here is the best kind of preventive mental hygiene at a simple physiological level.

"At least five different kinds of visits are offered in child health conferences: first, the complete physical examination visit made about once every three months in the first year of life and less frequently thereafter. Second is the inspection medical visit in between the physical examinations. The third type of visit is one merely for the completion of an immunization series. Fourth is the nursing home visit and fifth, in some child health conferences, the nurse holds conferences on a day when the physician is not present. The last two are made on a selective basis—on the recommendation of the physician, at the discretion of the nurse or at the request of the mother.

"With the increasing emphasis on the mental health aspects of child rearing, the traditional instructional type of interview between the mother and the doctor or the mother and the nurse becomes less appropriate. The two-way discussion in which the professional person does at least as much listening as talking is now beginning to appear. Since the interview has not been a prominent part of the professional training of the physician or the nurse, new techniques in the medical and nursing interview must be developed. For example, the classical rigid sequence of history taking, physical examination, immunization or other procedure must be modified and fitted into the total interview situation.

"For a good many years, sporadic efforts have been made to supplement the individual interview with group teaching. Studies are now under way on the most effective composition of groups of mothers and the methods of introducing group techniques into the child health conference. The scope of the group work is intended to be no broader than the usual content of the conference and the group sessions are to be carried by the regular conference staff.

"There is general recognition that the mere distribution of printed literature has little meaning unless it is done selectively in relation to the specific needs of the mother at the time and also unless the staff is fully acquainted with the contents of the printed material. The device is often used of having the nurse, who is the one who usually distributes the material, mark pages and paragraphs for special study by the family at home in connection with a question or problem. Careful use of posters and reading materials placed in waiting rooms is not common.

"While it is desirable to bring together the supervision of the well child and the care of illness, the latter is not usually held to be an appropriate activity in a child health conference. On the other hand, pediatric clinics which have heretofore usually limited themselves to the care and treatment of illness or health deviations can very easily add health supervision of well children to their program. When this is done, continuity can be attained by having the same personnel work in both services even though the health supervision may be given at a time different from care in the regular pediatric clinic.

"Increased emphasis upon well child care in hospital clinics would have a beneficial effect upon the training of hospital internes and resident physicians as well as upon the visiting staff. The Study of Child Health Services made by the American Academy of Pediatrics indicated widespread weakness in training in the care of well children, for pediatricians as well as for general practitioners.

"The Child Health Conference emphasizes to parents the importance of early medical care when illness occurs and also helps to refer the family to physicians for such care. Constant effort must be given to attaining continuity between health and sickness by procedures and practices which tie the Child Health Conference more closely to the private physician.

"Possibly in the future private practitioners and health departments will develop cooperative techniques for group instruction of parents and other joint arrangements for improving the health of children. Ways and means may be found by which the work of the practicing physician may be supported and extended by the services of public health nurses and health educators and by which may be made available to the private physician's patients some of the ancillary methods now used in the Child Health Conference.

"Of particular interest to the practicing pediatrician is the question of how many of the techniques of the child health conferences can be translated effectively to the private office. Can the office nurse, for example take a more active role in parent counseling and thus reduce the pressure upon the busy physician? Practicing pediatricians are also giving consideration to the possibility of introducing into their office routine group sessions with mothers and fathers, more effective use of printed literature and other educational approaches. It is particularly in the group practice of medicine that some of these techniques may lend themselves more readily to adaptation."

SAMUEL M. WISHIK, M.D.
Chairman, Committee on Child Health
Pittsburgh

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

STATISTICS FOR PREMATURE INFANTS

IN THE summary of the report of the Expert Committee on Prematurity of the World Health Organization, published in this column in February 1951, Dr. Ethel Dunham indicated the concern of the Expert Committee in regard to uniformity of information on the incidence and mortality of prematurity. The need for uniformity is particularly urgent in a field where there are so many intrinsic variable factors. It has been shown time and again that the ability of a premature infant to survive, under the best of care, is closely correlated with the birth weight, which in itself reflects the stage of maturity.[1] In turn, the stage of maturity at a given weight is affected by sex, race, and whether the child is a single or one of a multiple birth. Uniformly, at a particular stage of maturity, male infants are larger than female, single births are larger than multiple births and, in the United States, white babies are larger than Negro babies.

These considerations underline the danger of misinterpretation of so-called over-all rates for the incidence of prematurity and for the mortality of premature infants. For example, at any given weight, Negro premature infants are probably more mature and consequently have a better chance of surviving. Thus, hospitals in communities with a higher proportion of Negro than white babies will have an apparently lower total mortality rate than places where the reverse is true, even though the care is the same.

The danger is even greater in the presence of incomplete, inaccurate or unstandardized reporting. A hospital which fails to include in its figures the very small infants who die in the delivery room a few minutes or hours after birth will have an apparent mortality rate lower than the true one. Conversely, the hospital which does not count as premature the relatively larger infants who, while under 2500 gm., are vigorous enough to nurse at the breast and never enter the "premature nursery," will have spuriously high rates. Comparison of "total" rates, without detailed analysis, may thus lead to quite erroneous conclusions.

In addition to the work of the Expert Committee on Health Statistics of the World Health Organization, referred to by Dr. Dunham, a joint statement by the Association of Maternal and Child Health and Crippled Children's Directors and the Conference on Public Health Records and Statistics made specific recommendations for standardization of reporting. These have been summarized by Parkhurst and Schlesinger.[2] A more complete statement has been issued by the National Office of Vital Statistics and the U. S. Public Health Service, Children's Bureau, under the title "Recommendations for Developing Comparable Statistics on Prematurely Born Infants and Neonatal Mortality." Important excerpts follow:

"A. Definitions

"1. Live Birth and liveborn.—Live birth is the complete expulsion or extraction from its mother of a product of conception (irrespective of the duration of pregnancy) which,

after such separation, breathes or shows any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached; each product of such a birth is considered liveborn.

"This definition was recommended by the Expert Committee on Health Statistics of the World Health Organization, and adopted by the Third World Health Assembly in May 1950. It differs from the definition that appears in the 'Physicians Handbook on Death and Birth Registration, 1949,' mainly because of the phrases 'irrespective of the duration of pregnancy' and 'pulsation of the umbilical cord.' It is recommended that existing State laws or regulations be modified where necessary to reflect the changes in the definition.

"2. Immature (premature) infant.—For classification purposes, an immature infant is a liveborn infant with a birth weight of 5½ pounds (2500 gm.) or less, or specified as 'immature.' If weight is not specified, a liveborn infant with a period of gestation of less than 37 weeks or specified as 'premature' may be considered as the equivalent of an immature infant for purposes of this classification. (Number of weeks refers to completed weeks measured from the first day of the last menstrual period.)

"B. Completeness and Accuracy of Reporting on Birth and Death Records

"An important bias in the data on immaturity and neonatal mortality could result from failure of attendants to prepare birth and death certificates for infants who die immediately after birth. Every effort should be made, therefore, to secure the cooperation of attendants in the definition of live birth. A birth record should be filed even in those cases where there is no possibility of survival. If the infant dies at any time following birth, a death certificate should also be completed.

"1. Birth weight.—Accurate and consistent measurement requires that:

(1) The baby should be weighed immediately after delivery.

(2) The scale should be balanced before each weighing.

(3) Allowance should be made for any covering on the child or clamp on the cord.

(4) The birth weight should be noted and recorded to the nearest ounce or 10 gm. (do not round weights to the nearest pound or half pound).

(5) Accuracy of scales used in hospitals to weigh the newborn should be checked at intervals.

"2. Length of pregnancy (weeks).—For statistical purposes, period of gestation is defined as 'the number of completed weeks that have elapsed between the first day of the last menstrual period and the date of birth of the child.' It is recognized that there are cases where the exact date of the mother's last menstrual period cannot be determined accurately. However, the bias introduced by such errors will be relatively minor. From a statistical standpoint, the important factor is the consistent application of the definition on the basis of the best available evidence.

"At the present time, important inaccuracies are evident in gestational information derived from birth records. These arise principally from difficulties in computing 'length of pregnancy' in weeks, and are reflected in the statistics by extreme heaping at 36 and 40 weeks and a minor bias toward other even weeks. The heaping at 36 weeks is the result of incorrectly converting 9 calendar months (full-term gestation age) into weeks by considering 4 weeks the equivalent of a month. Heavy concentrations at 40 weeks are indicative in part of a failure to calculate period of gestation for the newborn infants who seem to be normally developed.

"Length-of-pregnancy data are potentially valuable for studying the broad problem of infant and fetal deaths and for distributing the 'not stated' birth weight group. In addition, improvement in reporting will make it possible to use the item jointly with birth weight to indicate the maturity of the newborn. This dual standard will be especially significant in examining the mortality experience of the groups near the borderline between maturity and immaturity as determined by birth weight alone.

"3. Complications of pregnancy and labor, operation for delivery, birth injury and congenital malformation.—One or more of these items appear in the supplementary 'medical and health' section of the birth certificate in about 40 states.

"4. Age at death.—Because the infant mortality rate changes sharply at the early ages, it is important to have the age of the infant recorded accurately. Age on the death certificate should be reported in 'hours' for infants under 1 day of age, in 'days' for infants under 1 month of age, and in 'months' for those over a month.

"5. Cause of death.—In the case of an infant, the cause of death is often difficult to determine. Such terms as 'congenital debility' or 'weakness,' 'immaturity,' and 'prematurity' are not in themselves satisfactory medical terms.

"C. Coding of Key Items on the Birth and Death Certificates

"It is essential that the items taken from the birth and death certificates be coded as consistently as possible from State to State and in sufficient detail to ensure valid and useful comparisons.

"D. Matched Birth and Infant Death Certificates

"Most States are routinely matching birth and infant death certificates. It is recommended that the data from these records be combined to obtain information on the survival of prematurely born infants during early infancy."

Efforts on the part of pediatricians and public health authorities leading to general adoption of these rules and definitions would go a long way toward achieving accuracy in the statistics of prematurity. With basically accurate reports and consideration of the problems of necessary corrections for incompleteness and differences between hospitals or areas of the country it will be much easier to measure achievement of standards and improvement in the care of premature infants.

REFERENCES

1. Baumgartner, Leona, Pessin, Vivian, Wegman, M. E., and Parker, Sylvia, Weight in relation to fetal and newborn mortality: Influence of sex and color, PEDIATRICS **6**:329, 1950.
2. Parkhurst, E., and Schlesinger, E. R., Basic data needed in planning programs for care of premature infants, Am. J. Pub. Health **41**:712, 1951.

SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

SKIN XANTHOMAS IN CHILDHOOD

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ALTHOUGH a number of discussions on the diagnosis and classification of skin xanthomas in adults are available,[1-3] comparable reviews of this problem in infancy and childhood have not been made. It is the purpose of this paper to make some suggestions regarding the study of pediatric patients with these lesions, utilizing reliable serum lipid analytic technics, and to summarize the somewhat limited knowledge concerning the etiology of most cutaneous xanthomas.

DEFINITION

The discussion will be confined principally to collections of xanthomatous material as found in the skin. Although the skin lesions represent only a portion of the whole problem, their presence often initiates diagnostic investigation. The word "xanthoma" was apparently first used (without definition) by W. F. Smith in 1869,[4] in describing a case of what appears to have been typical xanthoma tuberosum. Previously these lesions had been called vitiligoidea or xanthelasmas.

Xanthomas are best described as yellow or orange nodules in the skin (occasionally brownish or reddish). If histologic sections are made, the presence of intracellular sudanophilic material in abnormal quantity can be demonstrated. Differential staining of this intracellular material (e.g., the Schultz reaction[5]) will show a characteristic reaction for cholesterol, and tissue analysis will reveal a significant percentage of the lipid to be esterified or free cholesterol. For a lesion to be called a xanthoma, no further criteria are necessary (such as the functional origin of the storage cell or the presence of abnormal lipid levels in the patient's serum). In recent writing there has been a tendency to refer to any type of systemic disease with storage of lipid as a "xanthomatosis" (e.g., Gaucher's disease, in which cerebrosides are found). It seems more proper to limit the use of the term xanthoma to conditions in which there is chiefly an abnormal local collection of cholesterol.

PROCEDURE IN STUDY

A plan of investigation relating to lipid metabolism should be considered when a patient with a xanthomatous lesion in the skin is studied. This is necessary if treatment and prognosis are to be intelligently formulated. An accurate determination of serum total cholesterol is the single most valuable procedure. If this is normal, then the patient

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fits into the group with normal serum lipids, discussed under "Type I," below. If the cholesterol is increased analysis for the other lipid components (neutral fat, phospholipids and free cholesterol) is useful for classification. Further investigation of renal function, liver function, sugar metabolism, etc., may be indicated. Photographs of the lesions permit more careful comparison through the years, and pursuit of the details of family history is often pertinent. On occasion, roentgenologic survey of the chest and skeleton is advisable. In actual practice surgical biopsy to confirm the clinical impression of xanthoma is rarely necessary, except in the more obscure normocholesterolemic forms. A summary of the lipid analytic methods used for patients in this paper is given in table 1.

TABLE 1

ANALYTIC METHODS FOR SERUM LIPIDS, WITH AVERAGE NORMAL RESULTS

Determination	Method	Average normals*
Cholesterol	Schoenheimer-Sperry[6,7]	150–260 mg./100 cc.
Ester cholesterol	Free cholesterol from total, same method as above	65–75% of total cholesterol
Total fatty acids	Boyd's modification of Bloor[8]	
Phospholipids	Boyd's modification of Bloor[8]	150–250 mg./100 cc.
Neutral fat	Calculated from fatty acids not bound to cholesterol or phospholipid[8]	0–200 mg./100 cc.
Total lipids	Summation of neutral fat, phospholipids, cholesterol and cholesterol ester fatty acids[8]	400–800 mg./100 cc.
Carotenoids	May, Blackfan, McCreary and Allen[9]	3–75 "440 units"/100 cc.
Vitamin A	May et al.[9]	5–22 "620 units"/100 cc. ("blue units")

* For tables of pediatric normals, see Hodges, Sperry and Andersen[10] and Thomas.[11]

CLASSIFICATION OF CUTANEOUS XANTHOMAS

Type I. Serum Cholesterol (and Fats) Normal:

Group A. Xanthoma disseminatum (including those originally called "naevo-xantho-endothelioma" and juvenile xanthoma)

Group B. Xanthomas accompanying various chronic diseases, especially the "eosinophilic granuloma syndromes" or the so-called "reticulo-endothelioses" (including Hand-Schüller-Christian disease and Letterer-Siwe's disease)

Type II. Serum Cholesterol (and Fats) Elevated:

Group C. Xanthoma tuberosum (including essential familial hypercholesterolemia)

Group D. Secondary or eruptive xanthomas (including the transitory xanthomas of diabetes mellitus, idiopathic familial hyperlipemia, nephrotic syndrome, hypothyroidism, obstructive liver disease and von Gierke's disease)

TYPE I. SERUM CHOLESTEROL (AND FATS) NORMAL

Group A. Xanthoma Disseminatum. These simple skin xanthomas are both the most abundant and the most benign of the lesions under discussion.

Case 1. L. P. (Fig. 1), a female infant, had a 1.9 by 1.2 cm. orange plaque at vertex of scalp since birth and a 0.2 by 0.3 cm. bright orange nodule on chest wall since 2 mo. of age (Fig. 2). Past and family history noncontributory. Diet not remarkable. On physical examination a small yellow

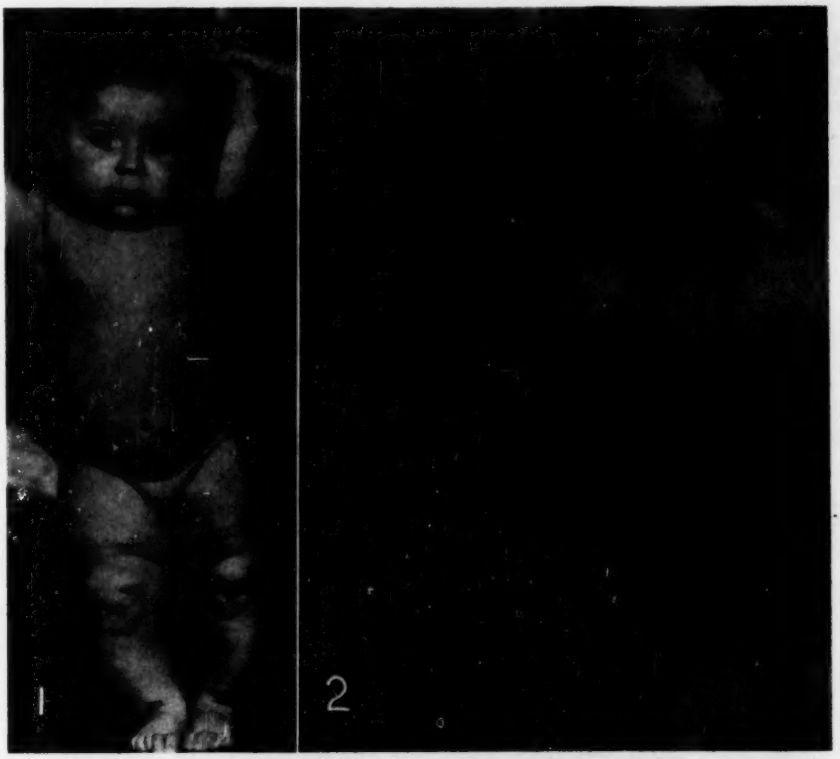

FIG. 1 (left). Case 1, 6 mo. of age. Xanthoma disseminatum. FIG. 2 (right). Case 1. Close-up of orange lesion on chest wall. This patient also had xanthomas on hard palate and scalp.

papule was also seen on hard palate, but no other abnormalities. RG films of chest, skull and long bones normal. Laboratory results normal (table 2). At age of 32 mo., with no special therapy, excellent general health continued and xanthomas were slowly getting smaller and flatter.

Case 2. M. G., 7 3/12 yr. old boy, had a 0.6 by 0.5 by 0.2 cm. orange nodule on buttock (Fig. 3)

TABLE 2

SERUM LIPID VALUES IN 5 CASES OF XANTHOMA DISSEMINATUM

Case No.	Total Lipids	Total Fatty Acids	Neutral Fat	Total Cholesterol	Ester Cholesterol	Phospho-lipid	Carotenoids	Vitamin A
	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	% of TC	mg./100 cc.	"440 units"/ 100 cc.	"620 units"/ 100 cc.
Normal	400–800		0–200	150–260	65–75	150–250	3–75	5–22
Case 1	741	464	230	175	61	269		
	379	122	0	182	72	104		
	657	390	169	192	78	198		
Case 2				296			26.2	18.7
Case 3	466	234	59	176	67	149	94.6	14.8
Case 4				274			139.	28.3
				285			128.	28.2
Case 5		205		250	73		61.	16.5

present for 8 mo. with slow recent increase in size but no local symptoms. No other lesions found. Family history negative. Cholesterol values were normal for patient and both parents. At mother's request lesion was removed surgically and showed abundant intracellular sudanophilic material (Fig. 4) that gave a deep purple staining with Schultz procedure. Incision healed with no new xanthoma formation in scar or elsewhere 15 mo. later.

Case 3. J. M., male infant, had tiny yellow papule observed at 3 wk. of age on side of forehead. It grew rapidly at first but then remained stationary. There was also a history of a few small orange papules under each eye. Past history otherwise negative and diet normal. Family history negative.

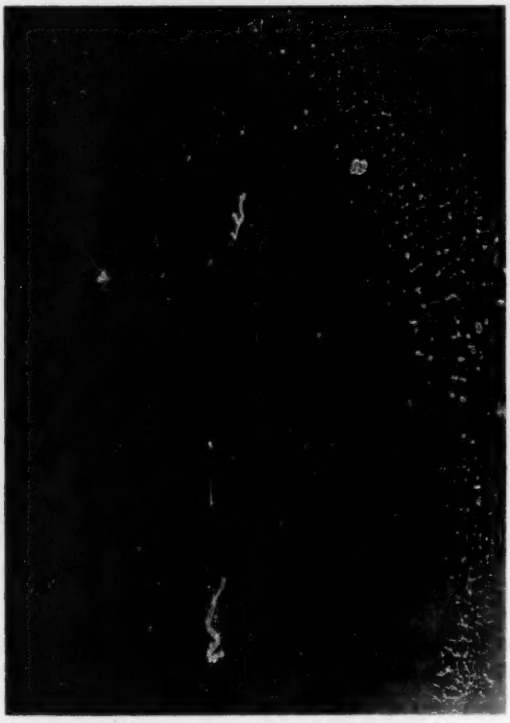

FIG. 3. Case 2. Xanthoma disseminatum. Close-up of lesion on left buttock. This xanthoma was removed surgically and microscopic anatomy is illustrated in Fig. 6.

Physical examination at 6 mo. of age showed a golden nodule, 0.3 by 0.3 cm., on forehead, but no other abnormalities. Serum lipids were normal except for carotenemia. At 2 yr. of age, xanthoma was conspicuously smaller and was duller in color. There were no new lesions and health remained excellent.

Case 4. F. W., male infant, had multiple orange papules and nodules apparently present since birth. Work-up elsewhere had included biopsy of a lesion, which was considered typical of xanthoma, a normal glucose tolerance test and negative films of skull, chest and long bones. Family history negative for xanthomata but father had diabetes mellitus. On physical examination at 16 mo. of age, patient was an active well-nourished infant with 3 xanthomas on scalp, one on L shoulder and one on forehead. There was a mild carotenemic tinge to skin and several faint brownish irregular pigmented areas. Biopsy scar had healed without new xanthoma formation. Laboratory examination showed normal cholesterol but high carotenoids. At 3 yr. of age, with elimination of high carotene-containing foods from diet, the lesions were all slowly fading with no new ones appearing.

Case 5. P. T., male infant, had tiny light orange papule appearing in front of ear at 7 mo. of age, which slowly enlarged and darkened. No local symptoms, but it bled when a doctor tried to "let the fluid out." Diet normal. Family history negative. Physical examination at 13 mo. showed a 0.3 by 0.3 cm. orange nodule, but no other abnormalities. Laboratory examination showed normal lipids, with mild carotenemia. By 26 mo. of age, lesion was lighter in color and flatter, no new xanthomas had appeared, and general health remained excellent.

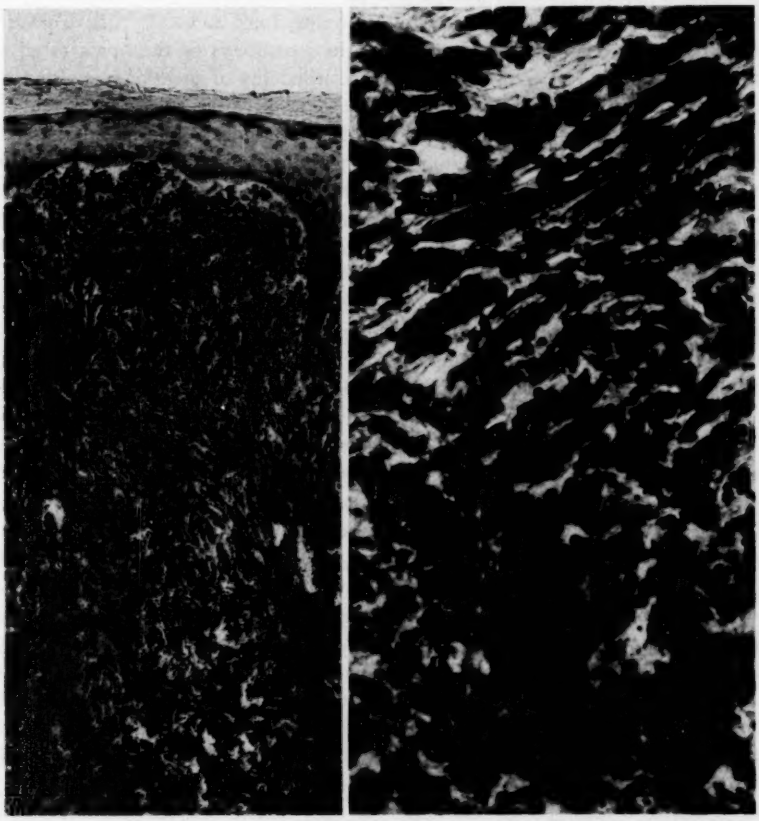

FIG. 4. Case 2. Xanthoma disseminatum. Low and high power views of microscopic anatomy with Sudan staining. Same lesion as illustrated in gross in Fig. 5. Note fibrous stroma and large numbers of sudanophilic intracellular droplets (shown black in photo). These same droplets took deep purple color with Schultz procedure.

These representative cases appear to be examples of the so-called "juvenile xanthoma."[12-14] Similar lesions have also been described under the names "naevo-xanthoendothelioma,"[15,16] "congenital xanthoma tuberosum"[17] and "xanthelasmatosis."[18] Most of the cases from the literature are in infants, the lesions showing abundant characteristic xanthoma cells when biopsied, the serum cholesterol values being normal when reported, and the natural history of the lesions being comparable to that observed in the cases reported here.

In order to discuss the inter-relations between these synonyms and the most likely common etiology involved, a few words about the basic pathogenesis of the xanthoma cell seem necessary. Theories regarding the formation of lipids in endothelial or connective tissue cells are diverse. When the serum lipids are markedly elevated (see cases in Type II), it is difficult to refute the notion of deposition in scavenging cells, but in the cases under discussion the major fractions of the serum lipids have been repeatedly found normal (table 2). Even with the total lipids normal, some authors[19, 20] have pointed to small variations in the ratios between the various partitions of the lipids (e.g., phospholipids, neutral fat) as indicating a "relative instability of the blood emulsion which favors the formation of xanthomatous deposits."[20] Such detailed interpretation of the rather inaccurate results from most available lipid methods seems unjustified, and the evidence is not convincing. Furthermore, serum lipids are no longer considered simple "fat-in-water emulsions" as originally conceived, but have a more stable and intimate relationship with the blood proteins, as exemplified by the lipo-protein complexes. Investigation based on these new physical concepts gives promise of being more productive.[21]

Since the theory based on the concept of overflow from the serum lipids is unsatisfactory for the normocholesterolemic xanthomas, a number of authors have pointed out the ubiquity of the xanthoma cell in many types of pathologic processes.[22–26] Abscesses, cysts, exudates, necrotic lesions, and especially tumors of many regions of the body are not uncommonly associated with xanthoma cell formation, in the presence of normal serum lipids. The organs where this most commonly occurs are the breast, Fallopian tubes, thyroid, testis, kidney, gall bladder, bone marrow, brain, peritoneum and blood vessels. One thus derives the impression that the xanthoma cell joins with the polymorphonuclear leukocyte and the fibroblast as a manifestation of the body's limited apparatus for "reaction" to varied types of acute and chronic stimuli. To return more specifically to the skin, Gross and Wolbach[27] have discussed the formation of xanthoma cells and the deposition of iron-containing pigment in "sclerosing hemangiomas." Some of the factors which might be operative in these cases of xanthoma disseminata or "juvenile xanthomas" could then be nonspecific. A few have a history of a reddish lesion first, indicating a possible healing hemangioma. Other benign skin tumors could be the origin for some. Although the name "naevo-xantho-endothelioma" should probably be dropped, it may have arisen from the origin of some of the xanthomas in endothelioma-like lesions. Foot[28] considered some xanthomatous lesions as related to the melanomas.

There seems to be a special predilection of these simple skin xanthomas for infants. In many of the reports, the lesions appear to have been formed before birth or to have arisen in the first few weeks of life. No studies have been found in which the course of these lesions has been followed from infancy into adult life, but on a nosologic basis they appear to be the pediatric equivalent of the uncomplicated "xanthoma disseminatum" of adult dermatology texts. Since many cases (e.g., Cases 1 and 4, as reported here) are indeed disseminated, and since the term xanthoma disseminatum has become synonymous in dermatologic usage with an innocent xanthomatous skin lesion with normal serum lipids and no other visceral involvement, it seems that this is the preferred terminology for these cases.

One other aspect of pathogenesis that is poorly understood is the relationship to carotene. Note that the blood carotenoids are normal in one, high normal in one, and markedly elevated in two of the cases reported here (table 2). Furthermore, it has been

suggested[23] that since both cholesterol and its esters are colorless, these "yellow tumors" must be colored by a pigment of similar solubility, presumably carotenoids. Why these patients have a greater than average tendency to deposit carotene is not obvious. Inasmuch as vitamin A levels are usually normal, it is not likely that failure of hepatic conversion of carotene can be implicated.

In spite of these conjectures it should be pointed out that the etiology of most cases of xanthoma disseminatum is completely unknown.

Diagnosis

The diagnosis of a xanthomatous lesion as "xanthoma disseminatum" is largely one of exclusion. Having demonstrated the serum cholesterol to be normal, a careful clinical evaluation is necessary to rule out generalized xanthomatosis (Hand-Schüller-Christian disease), as described in "Group B" below. With a characteristic solitary lesion, this ordinarily presents no problem. The patient is a robust, active, normally-growing infant with no other symptoms (Fig. 1). He typically has a discrete bright orange nodule on his trunk or face that has been present without much change in size for several months. Physical examination is otherwise negative. Occasionally, however, the lesions assume a reddish papular form or a flat, golden-brown macular configuration, and may be quite numerous. With multiple lesions, and in any suspicious case, a chest roentgenogram, skull or other bone films, and a more careful follow-up may be indicated. Family history is typically negative.

Prognosis

There is no reason to believe that the prognosis of xanthoma disseminatum is other than excellent. As stated above, reports of cases with a long-term follow-up are lacking, but in the cases in this study that have been watched for 2 to 3 years there has been a tendency to slow spontaneous disappearance of the lesions. If visceral involvement was not demonstrated at the time of the initial work-up, it has not appeared subsequently. While careful checking at intervals is indicated, the parents can be reassured that there is no cause for alarm. The lesions are neither malignant nor the warning signs of irreversible internal processes.

Treatment

There is no definitive treatment for xanthoma disseminatum. Outpatient department or office visits every 3 to 6 months with occasional blood chemical studies are the responsibility of the physician following the case. The two questions which repeatedly arise concern surgical removal and dietary management. Certainly there is no contra-indication to surgical removal of the solitary lesion if it is a cause of great concern to the parent or child, or is at an area of repeated trauma. This will allow pathologic examination and further reassurance. However, the tendency of these lesions to disappear spontaneously (with possible recurrence elsewhere) makes removal unnecessary. Some authors[18] have observed new xanthoma formation in the scar from biopsy. If these lesions are multiple, surgical removal (beyond biopsy, if felt necessary) is especially inefficient. As far as dietary restriction of cholesterol- or carotene-containing foods is concerned, there appears to be no rationale for this unless the diet is grossly abnormal. It has been the author's practice to observe these patients at approximately six month intervals, with a diet normal for age.

Group B. Xanthomas Accompanying Chronic Disease, especially the "eosinophilic granuloma syndromes" (generalized xanthomatosis, etc.).

Although a similar etiology may exist for the skin xanthomas discussed in the "xanthoma disseminatum" group above, and the foam-cell deposits in the skin and viscera of the generalized xanthomatosis patients, the natural history of the disease is so different that it warrants separate classification. Here again, examination of the serum reveals no gross alteration of the lipid components, including cholesterol (table 3). In this group, however, there is widespread, usually progressive involvement of the body with a disease process that could well lay the groundwork for xanthoma cell formation, as was discussed in the previous section.

TABLE 3

SERUM LIPID VALUES IN 3 CASES OF LETTERER-SIWE'S DISEASE

Case No.	Total Lipids	Total Fatty Acids	Neutral Fat	Total Cholesterol	Ester Cholesterol	Phospho-lipid	Carotenoids	Vitamin A
	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	% of TC	mg./100 cc.	"440 units"/ 100 cc.	"620 units"/ 100 cc.
Case 6	592	365	139	143	83	230		
Case 7	626	302	71	267	71	161		
Case 8				136	71		13.1	16.3

1. Eosinophilic Granuloma Syndromes: The concept of Farber[29] regarding the quantitative rather than qualitative differences between eosinophilic granuloma, generalized xanthomatosis and reticuloendotheliosis, and their common origin in the granulomatous process, possibly infectious, rather than a lipid-metabolic disorder, is gaining wide acceptance. However, as has been amply demonstrated, the extent of cholesterol deposition and foam cell formation can be spectacular in some stages of the disease. Cowie and Magee[30] found the xanthomatous masses of a case of generalized xanthomatosis to contain 7 to 7.5% lipid (wet weight), of which more than half was cholesterol. These appear to be typical figures. Discherl[31] discusses a lesion of the dura mater that contained 15.4% esterified cholesterol (dry weight) and 3.2% free cholesterol. Rowland[32] says that the yellow lesions of generalized xanthomatosis contain phosphatides, neutral fat and free and esterified cholesterol, but gives no figures. Thannhauser[33] is concerned that foam-cell formation should be so marked in these lesions while relatively infrequent in necrotic or infectious lesions of other conditions. Although, as discussed above, formation of xanthoma cells is indeed a widespread nonspecific phenomenon, it must be admitted that in these disease conditions under discussion the tendency has become extremely prominent. Of great interest is the observation of Biedermann and Höfer[34] that in tissue cultures from Hand-Schüller-Christian lesions, foam cell formation is marked, and reminiscent of the *in situ* pathology. This phenomenon is apparently different from the degenerative fat phanerosis of poorly-cared-for tissue cultures. There appears to be a strong directive force toward local lipid formation—perhaps inherent in the individual's cells (see Thannhauser,[12] p. 353), perhaps related to the specific toxic effects of some infecting organism.

The special significance of skin xanthoma formation in generalized xanthomatosis and reticuloendotheliosis cases is not clear. The most acceptable view seems to be that the skin

lesions are merely one of the large group of manifestations of a basic process, often called "reticuloendotheliosis" or "reticulogranuloma."[35] These various changes include hepatomegaly and splenomegaly (usually without lipid storage), generalized lymphadenopathy, pulmonary infiltrations, bone marrow proliferation with bone destruction, xanthomatous collections on the meninges, skin and elsewhere, and a scaling, petechial eruption on the skin. The terminology depends somewhat on the grouping of signs and symptoms, and the course of the disease, with poor general agreement in the literature between different authors. Skin xanthomas may be seen in both the severe, rapidly fatal cases ("Letterer-Siwe's disease," see Case 6), or in the milder forms of the syndrome (e.g., Case 8; see also Case 43 in Thannhauser[12]), but tend to be typical of the chronic prolonged case.

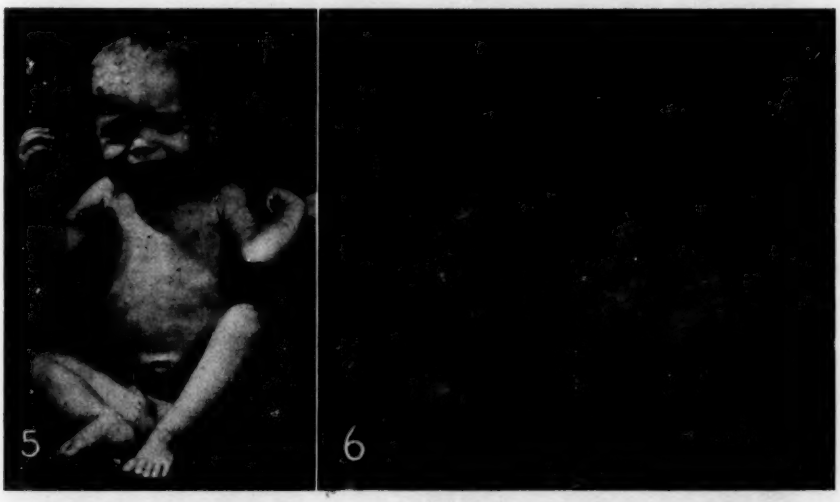

FIG. 5. Case 6, 15 mo. of age. Reticuloendotheliosis disease with xanthoma. FIG. 6. Case 6. Close-up of yellow nodules on forehead. Lesion from this child was biopsied and is illustrated in Fig. 9.

Case 6. T. S., male infant, had had multiple pea-sized nodules on scalp and elsewhere since age of 3½ mo., appearing first as red papules resembling small furuncles. He had also had several pathologic fractures. Physical examination at 11 mo. showed a small poorly nourished infant (Fig. 5) with many large xanthomas (Fig. 6). A skin biopsy confirmed this impression (Fig. 7). Bone RG showed many defects. Blood lipids were normal. Reticuloendotheliosis was considered the most appropriate diagnosis. While under the care of the Tumor Therapy Service, he received aureomycin, nitrogen mustard and folic-acid antagonists, with no change in general appearance or histology of lesions. At 15 mo. of age, he developed varicella, with rapid progression and hemorrhagic necrotic lesions and died at the height of this disease. Autopsy showed extensive visceral involvement by both lipogranuloma and varicella.

Another fatal case (Case 7, K. R., female, 3 7/12 yr. of age, see table 3) had no visible cutaneous xanthomas, but on biopsy of the petechial eruption, microscopic examination showed a granulomatous formation that lacked only the sudanophilic storage to resemble the "lipogranuloma" of Case 6. The following case had visceral involvement, but has been followed for 2 yr. without definite evidence of progression:

Case 8. J. B., female. Beginning at 9 mo. of age, soft orange lesions appeared on forehead, arms, back, shoulders and groin. These came and went over a period of many months, but were never seen on elbows, knees, heels or eyelids. At 1 9/12 yr., she was first seen here. Family history was negative. Physical examination showed marked enlargement of liver and spleen, scattered xanthomas and generalized lymphadenopathy. Serum cholesterol was 145 mg./100 cc. Liver function studies gave positive flocculation reactions. Chest film showed diffuse granular increased density, consistent

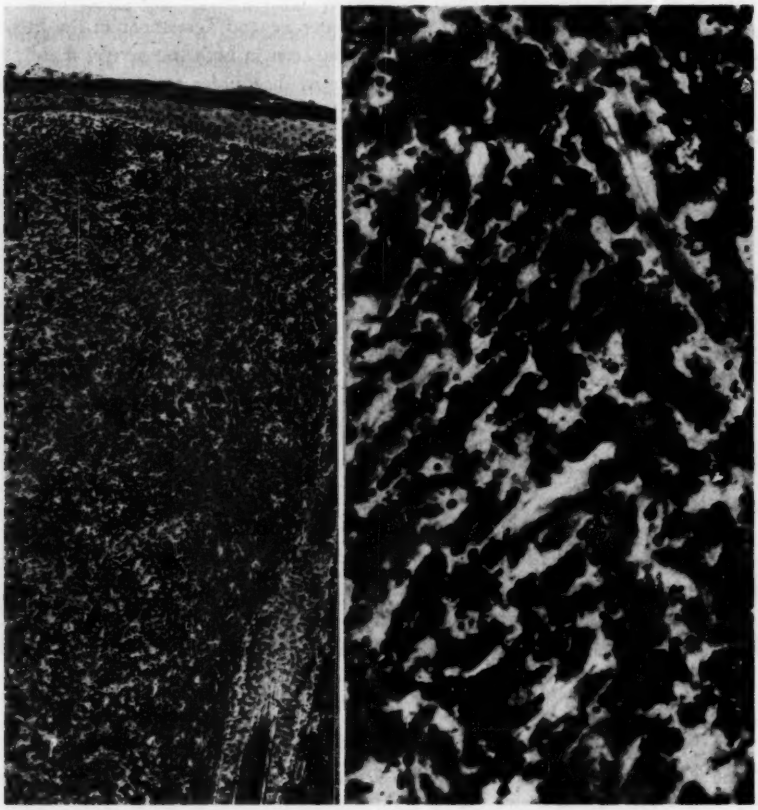

FIG. 7. Case 6. Reticuloendotheliosis with xanthomas. Low and high power views of microscopic anatomy of skin lesion with Sudan staining. Note marked similarity to lipid deposition of xanthoma disseminatum lesion (Fig. 6). Intracellular droplets of this case also took deep purple color with Schultz procedure for cholesterol.

with reticuloendotheliosis. Biopsy of skin and lymph node revealed lipid-containing cells. With supervision in outpatient department, general progress has been good. Skin xanthomas have continued to come and go. There have been no respiratory symptoms. Lymphadenopathy and visceral enlargement have persisted. On readmission at 3 1/12 yr. of age there were superficial skin infections (Fig. 8) probably not related to xanthomas but producing an orange exudate, and an apparent acute glomerulonephritis. Golden xanthomas were still present, especially in the groin (Fig. 9). The cell count was persistently elevated. Bone marrow was not remarkable. Skin biopsy again was confirmative of xanthoma. Bone RG still showed no lesions, but lung fields contained a similar amount of infiltration. Blood lipids were normal (table 3). A follow-up visit at 3 8/12 yr. of age

revealed no significant changes in general status. This is an unusual case, with a completely indefinite prognosis.

2. Other Types of Patients: When the multiple causation of xanthoma formation is recalled, it seems reasonable to expect the appearance of these lesions in a wide variety of systemic diseases. The author has observed diffuse xanthomas forming during leukemia in a 10 month old boy (serum lipids not measured) and early in the course of von Recklinghausen's neurofibromatosis in a 9 year old girl (total serum cholesterol 226 mg./100 cc.). The relationship of the xanthomas to these diseases is obscure, but other examples of similar cases will undoubtedly appear as observations continue.

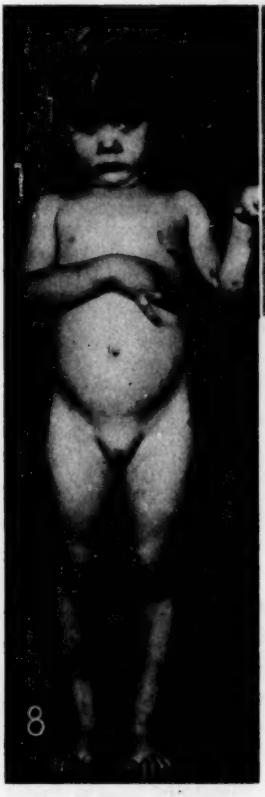

FIG. 8. Case 8, at 3 1/12 yr. of age. Reticuloendotheliosis with xanthoma. Note superficial skin infections on knees and elbows. FIG. 9. Case 8. Close-up of xanthomas in groin. One of these lesions was biopsied and showed characteristic xanthoma histology.

DIAGNOSIS

Any positive finding on physical examination in a patient with normocholesterolemic xanthomas deserves careful investigation. Enlargement of the liver or spleen, lymphadenopathy, irregularities in the skull, other types of skin lesions, respiratory symptoms, etc., serve as indication for bone and chest RGs. Typically these patients show evidence of chronic disease, as opposed to the chubby happy child whose lesions are limited to the skin only, but milder forms (e.g., Case 8) demonstrate the need for vigilance if

correct appraisal is to be made. Biopsy of the skin, lymph nodes or bone marrow may be required. Family history is noncontributory.

Prognosis and Treatment

It is beyond the scope of this paper to discuss the management of these patients once further disease beyond the skin xanthomas has been demonstrated. Surgical removal or dietary restriction is not indicated.

Type II. Serum Cholesterol (and Fats) Elevated

Group C. Xanthoma Tuberosum Group. Less frequent than patients with xanthoma disseminatum in the pediatric age range, but more seriously ill, are those with xanthoma tuberosum. In the records of the Children's Medical Center only two cases could be found

TABLE 4

Serum Lipid Values in Xanthoma Tuberosum (Case 9) and in 6 Cases with Secondary Xanthomata: Diabetes Mellitus (Case 10), Idiopathic Familial Hyperlipemia (Case 11), Nephrotic Syndrome (Cases 12 and 13), Chronic Obstructive Liver Disease (Case 14) and von Gierke's Disease (Case 15)

Case No.	Total Lipids	Total Fatty Acids	Neutral Fat	Total Cholesterol	Ester Cholesterol	Phospho-lipid	Carotenoids	Vitamin A
	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	% of TC	mg./100 cc.	"440 units"/ 100 cc.	"620 units"/ 100 cc.
Case 9	2,840			670				
	2,620			606				
	2,260			782				
Case 10	19,383	16,550	15,600	1,340	29	2,180	131.6	
Case 11	6,252	5,088	4,650	740	55	592		
	3,003	2,448	2,265	304	14	406	23.5	50.9
Case 12	5,679	4,100	3,220	1,156	65	796	127.6	43
Case 13				1,180	66		215	176
Case 14	1,264	394	0	575	35	556	20.5	8.8
Case 15	2,214	1,636	1,382	428	54	248	139.8	36.5
	5,318	3,656	2,630	1,226	68	900		

which qualified for this diagnosis. Cook et al.[36] have collected 20 cases with cardiac complications in the younger age ranges and added one of their own; Rigdon and Willeford[37] discussed nine cases of sudden death in childhood with this disease. Many other reports have appeared, typically of older children and young adults. Flat lesions in the same group are called "xanthoma planum," and the name "xanthoma multiplex" also usually applies to this hypercholesterolemic group.

Case 9. R. B., male. This patient, originally studied by Dr. Harry Shwachman, began to develop yellow nodules in skin at 6 mo. of age—appearing first on dorsum of left foot, then at base of spine, on achilles tendon, elbows and upper arms. They increased slowly in size and number with no local symptoms. Past history had been otherwise negative. Family history was negative and examination of relatives' serum showed values for total lipids of 1102, 1130 and 898 mg./100 cc., and for total cholesterol of 223, 308 and 224 mg./100 cc. on the father, mother and brother, respectively. Physical examination at 3½ yr. of age showed nodules as mentioned (Fig. 11) and a small but otherwise well boy (Fig. 10). Laboratory examination showed elevated lipids (table 4). Skull, chest, pelvis and long bone RGs revealed no abnormalities and a glucose tolerance test was normal. A low fat diet was recommended but produced no notable change in the lesions or blood lipid

levels over a 5 mo. period. Eye changes resembling "arcus senilis" were observed on a follow-up visit.

Contact was lost with patient, but Dr. Frank N. Allen of the Lahey Clinic informed the author that patient was seen there at age of 8 11/12 yr., following 8 mo. of precordial pain. Examination then showed cardiac enlargement, early congestive failure and electrocardiographic changes. Cholesterol at that time was 699 mg./100 cc. He died 4 days later following a 12 min. attack of anginal pain.

Discussion of etiology is complicated by the constant finding in these patients of an elevated serum cholesterol. Furthermore, it has usually been possible to discover relatives of patients with xanthoma tuberosum who have hypercholesterolemia without actual xanthomas ("essential familial hypercholesterolemia"[1]). Many attempts have been made to work out the genetics of this condition, and the elevated serum cholesterol emerges

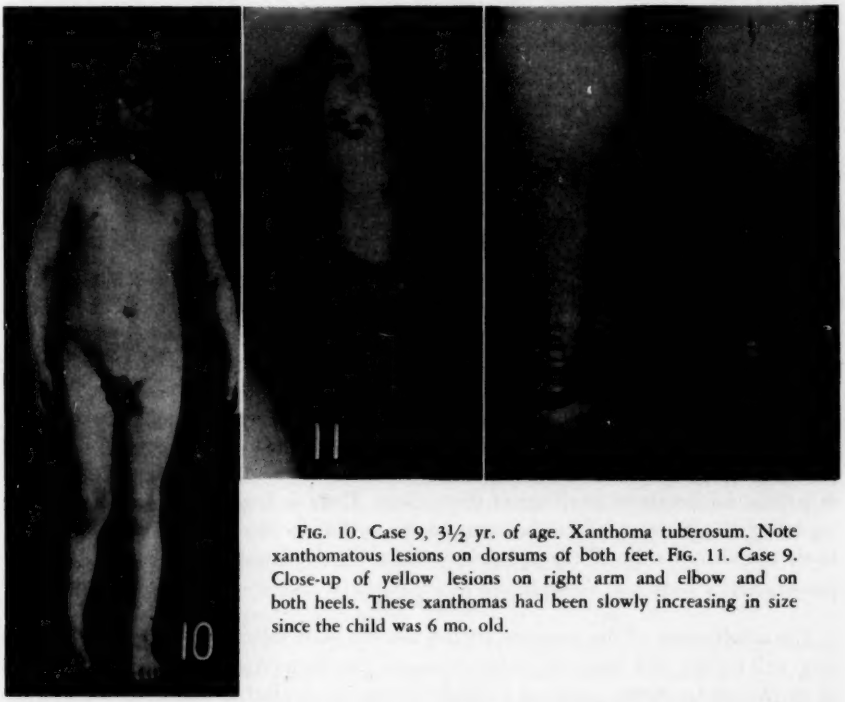

FIG. 10. Case 9, 3½ yr. of age. Xanthoma tuberosum. Note xanthomatous lesions on dorsums of both feet. FIG. 11. Case 9. Close-up of yellow lesions on right arm and elbow and on both heels. These xanthomas had been slowly increasing in size since the child was 6 mo. old.

as the most constant factor, suggested by Svendsen[38] as a dominantly inherited factor, and by Fliegelman et al.[39] as an "incomplete dominant trait." Aldersberg et al.[40] (as well as Fliegelman) have arrived at the picture of a hereditary disturbance of cholesterol metabolism, with late coronary atheromatosis as a milder heterozygous form, and with tuberous skin xanthomas and early arterial changes as well, as the severest homozygous state. Thannhauser[41] feels that the blood vessel lesions in this syndrome are best described as atheromata, and distinct from the diffuse degenerative picture of arteriosclerosis. Montgomery, in a discussion of Fliegelman's paper,[39] points to the observation that valvular heart lesions (especially involving the mitral valve) are more common

in children with this syndrome, as opposed to the situation in adults where only coronary lesions are usually found.

Pollitzer and Wile[42] give an excellent description of the pathology of the xanthoma tuberosum lesion, obtained by sampling skin lesions at different stages of maturity in a single patient. The earliest changes they saw appeared in the adventitial connective tissue cells of the smallest blood vessels (in areas where trauma and skin stretching were prominent). These cells were said to take up the lipid which is present in excess in the blood, proliferate and increase in size to form xanthoma cells. They conceived of this process as an "irritative connective tissue hyperplasia." This lesion then becomes surrounded by a fibroblastic reaction, which, combined with a saturation of the cells near the blood vessels with lipid, allegedly serves as a self-limiting check on the size of the xanthomatous lesion.

It has been demonstrated that the elevation of cholesterol is the most prominent feature of the altered serum chemistry and indeed, the level of this substance usually ranges from 350 to 1000 mg./100 cc.[12,43,44] There is commonly a moderate increase in phospholipids. Large increases of neutral fat are less frequent, but the neutral fat figures are usually somewhat increased.

Chaikoff et al.[45] tested alimentary lipemia following olive oil meals in a 27 year old patient with xanthoma tuberosum compared with a group of normals, and found no obvious abnormality of fat absorption and storage. Thannhauser[12] analyzed a xanthoma tuberosum lesion and found 5.5% cholesterol (45% esterified) wet weight and 2.0% phospholipid.

Diagnosis

The increased cholesterol value in the serum immediately gives warning that the xanthomatous lesions may belong to the xanthoma tuberosum group. When full-blown the picture is characteristic (see Fig. 1[1]) and easy to diagnose. Large, soft, golden or brownish nodules on the elbows, knees, buttocks and heels are the most common, with less tendency for involvement of the trunk and face than in the patients with xanthoma disseminatum. The palms and knuckles may also be involved, and it may be possible to palpate xanthomatous swellings of the tendons. There is disagreement in the literature regarding the presence of xanthelasmas of the eyelids in this syndrome, but it is certainly not characteristic of the pediatric patients.[46,47] A positive family history is usual.

Prognosis

The involvement of the coronary arteries and the heart valves with lipid deposition is now well known, and causes the greatest concern regarding prognosis. This would appear to be the most common cause of coronary disease in childhood. The collected data of Cook et al.[36] and of Rigdon and Willeford[37] show the frequency of sudden death with this pathology. Careful cardiac evaluation is certainly indicated and great caution necessary in prognostication. One gets the impression that in fully developed xanthoma tuberosum the prognosis for normal life expectancy is only fair to poor, but that there are many less severe "subclinical" cases with good prognosis.

Treatment

Restriction of the intake of high cholesterol foods appears sensible since the serum cholesterol level seems to be intimately involved in the production of lesions. The results are not dramatic, however, probably in part because of the ability of the human body to

manufacture cholesterol endogenously from short-chain carbon compounds. Brain and egg-yolk (⅓ gm./yolk) are the only foods with more than 1% cholesterol content,[48] but milk contains about 100 mg./quart and liver and other animal foods contain definite amounts. Since cholesterol must be absorbed in the presence of neutral fat,[49] restriction of all fat is probably worth while. Thannhauser[12] discusses low cholesterol diets in some detail. Different authors have adopted different degrees of strictness in this regard. Sperry and Schick[47] describe an 11 year old patient treated on an egg-free diet for two years with a serum cholesterol level of 810 to 950 mg./100 cc. One month of a diet exclusively from plant sources made no difference in blood chemistry, and at the end of one year on this plant diet plus 500 cc. of skimmed milk daily, the serum cholesterol was still 765 to 853 mg./100 cc. Various "lipotropic" substances have been tried without success. Curtis and Berger[50] used lecithin, cephalin and inositol mixtures for periods of several months on patients with xanthelasmas and elevated serum cholesterol levels without effect, and Schmidt[51] used cholesterol-free diet, liver injections, adrenal cortical preparations and insulin ineffectively with a xanthoma tuberosum patient. Delevett and Bruger[52] tried vitamin E, lecithin, lipocaic and pancreatic extract with no effects on nine patients with xanthoma tuberosum.

Other treatment is symptomatic, especially regarding the cardiac status. Surgical removal of lesions in this condition, sometimes called "lipid gout" in the older articles, would be as futile as removal of large tophi in "uric acid gout" (unless they presented a mechanical problem).

Group D. Secondary Xanthomas.

An interesting insight into the pathogenesis of the xanthoma cell is given by the "eruptive" or secondary type of xanthoma. As has been well documented by Thannhauser,[12] almost all conditions characterized by a chronic hyperlipemia have a tendency to the formation of small, transitory xanthomatous eruptions on the skin. The predilection for this phenomenon, however, does not seem to be a direct function of the degree of elevation of the serum lipid level involved, once a certain minimum is exceeded. As in the case of xanthoma tuberosum, formation of the lesions cannot be considered separately from the fact that the blood lipids are elevated, and it is tempting to assume that simple scavenging of this increased lipid is the basic process, or possibly a saturation of the mechanism for normal metabolism and turnover of lipids.

Those diseases most commonly associated with hyperlipemia, and thus with secondary xanthomas, are as follows:

1. Diabetes Mellitus: Lipid levels in the serum, including that of cholesterol, are usually slightly elevated in diabetes, and occasionally very much so. Some patients with relatively low insulin requirements have strikingly elevated serum lipids, but the most impressive figures reported for hyperlipemia in diabetes are those cases with poor control, severe acidosis, and coma or near-coma. Prompt lowering of the lipid values ensues when acidosis is relieved and the diabetes controlled. Total serum lipid levels of 14.1%,[53] 14.9%,[54] 19.86%[53] and 20.6%[55] have been listed for diabetic patients in critical condition. As can be seen, these are the highest levels found in any disease. Eruptive xanthomas ("xanthoma diabeticorum") are common in such severe cases, but are transitory in nature and are not seen in most juvenile diabetic patients.

Case 10. R. D. This female patient (Fig. 12) was well until the age of 11 8/12 yr. when she had fatigue, polydipsia and mild hyperglycemia. She was placed on a restricted carbohydrate intake,

obtaining approximately 48% of her daily calories from fat. She improved symptomatically and was seen here first at the age of 12 8/12 yr. with a 2 day history of midabdominal pain and fatigue, followed by vomiting and grogginess. Past history had been otherwise negative. Skin lesions had not been noted by her parents. Family history was negative and the parents' serum cholesterols were normal. Physical examination on admission showed coma, fever, hyperpnea, right lower lobe pneumonia, palpable liver, severe lipemia retinalis and several dozen bright orange papules, many

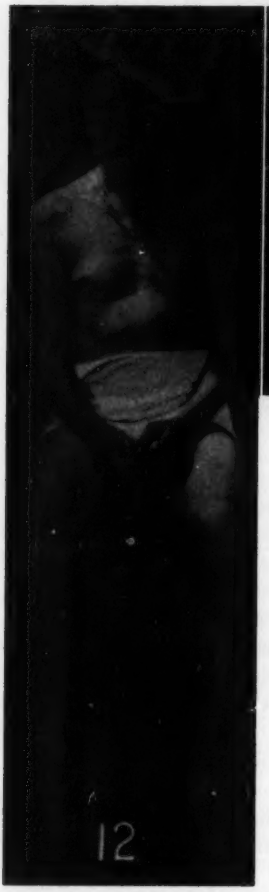

FIG. 12. Case 10, at 12 8/12 yr. of age. Diabetes mellitus with secondary xanthomata. Photo taken just after recovery from severe diabetic coma. FIG. 13. Case 10. Close-up of orange nodules on knees. These xanthomas disappeared promptly on insulin therapy.

of them excoriated, on the face, arms, groin and knees (Fig. 13). A recent scratch of the forearm had healed with an elevated orange scar. Her laboratory work was consistent with severe diabetic acidosis (urine 4+ for sugar and acetone, blood carbon dioxide 5.0 mEq./l.). She responded satisfactorily to insulin, parenteral fluids and antibiotics. She was discharged on 10 units of protamine insulin and 20 units of regular insulin daily. Her control in the outpatient department was fair, with some increase needed in the regular insulin. Her xanthomata were almost gone on discharge and completely gone in 8 wk. at which time her serum cholesterol was 337 mg./100 cc.

The large experience of the Joslin group was summarized by White.[56] Of 14 patients found with xanthoma diabeticorum, lesions appeared before the age of 20 in 7, none before the age of 12 years. The serum cholesterol levels reported for this group averaged

937 mg./100 cc. Major[57] collected 74 cases of xanthoma diabeticorum at all ages from the literature in 1924 and added three new ones. One was a 16 year old boy whose serum cholesterol was 400 mg./100 cc. Following two mosquito bites, two small inflammatory nodules were produced and "a few days later a deposit of yellowish orange pigment appeared and the nodules became quite hard." Under insulin therapy these xanthomas promptly disappeared.

2. Idiopathic Familial Hyperlipemia (Buerger-Grütz Syndrome): This benign syndrome, originally considered quite rare, is being discovered with increasing frequency as laboratory examination of the blood becomes more widespread. The admitting "symptom" is usually the discovery that the blood is so creamy as to prevent hemoglobin estimation. This severe lipemia is the single most constant feature. Sometimes the liver and spleen are enlarged, but in the single postmortem examination available[58] there was no notable lipid storage. There is a tendency to fluctuation in the severity of the lipemia, occasionally associated with abdominal pain at the peak of the rise.[59] It has been suggested that many of the cases reported as "chronic pancreatitis with hyperlipemia" may be identical with this syndrome.[60] Carefully reported metabolic studies have yielded no significant etiologic suggestions,[59, 61] although Thannhauser and Stanley[62] consider the condition a "retention lipemia," on the basis of feeding radioactive iodized olive oil. Simple lowering of dietary fat will regularly produce a marked lowering of serum lipids, but it is difficult to get continued cooperation from the patient and parent because of the absence of subjective symptoms. Most of the early cases reported have been in children, but more adult cases (otherwise well) are being uncovered,[12, 63] and the prognosis is apparently excellent. Secondary xanthomas are frequent, as would be expected, with reported serum total lipid figures from 3 to 9%, in great part made up of increases of neutral fat.

Case 11. H. G. A female infant referred by Dr. Fred Allen of Holyoke, Mass. The patient was noted on routine office hemoglobin examination to have blood which resembled "tomato bisque," while several weeks earlier it had appeared normal. Serum lipids at that time (11 mo. of age) were 6.2% (see table 4). She was given no special therapy and had no symptoms. Past history was negative except for a bout of otitis media and considerable anemia. Family history was negative. Physical examination at 17 mo. of age (Fig. 14) showed a chubby, good-looking infant with a half dozen orange papules on the right lower leg. (Fig. 15) and 12 to 15 across the back of the shoulders and upper chest. There were no other abnormalities noted. Laboratory examination showed serum lipids of 3.0% (table 4), normal urine, red blood cell count of 4.2 million, serum proteins of 6.04 gm./100 cc. with 4.9 gm. of albumin, and blood glycogen value was 0.72 mg./100 cc. (measured by Dr. Richard Wagner of the Boston Floating Hospital, who considered this value normal). Oral glucose tolerance test was normal. The patient's general progress has continued to be good, with only minimal restriction of dietary fat. At 2 9/12 and at 3 3/12 yr., the serum was still grossly lipemic and many skin xanthomata were present.

3. Nephrotic Syndrome: "Lipoid nephrosis," as in the nephrotic syndrome of childhood or as the nephrotic stage of chronic glomerulonephritis, is associated with periods of extreme hyperlipemia. Even the collections of fluid in the body chambers are fatty. In remission, patients with the nephrotic syndrome usually have completely normal serum lipid values. It is rather puzzling why secondary xanthomas should be so uncommon in the nephrotic syndrome. The transitory nature of the relapse must be partly responsible, but in the face of such high levels reached even briefly it would seem reasonable to expect frequent xanthomas. The only instance of xanthoma formation in a pediatric patient with nephrosis that was noted in the literature is that of Friedman et al.[64] but two additional cases are submitted below, in one instance proved by biopsy examination.

Case 12. R. D. had been well until the age of 2 9/12 yr. when, following a mild respiratory infection, generalized puffiness developed. When seen then, he had albuminuria, small numbers of cellular elements in the urine and a total serum cholesterol of 610 mg./100 cc. A mild diuresis occurred, but more severe and persistent fluid accumulation took place while on a diet abnormal only in that excess salt was restricted. Past history and family history were noncontributory. Physical examination at 3 1/12 yr. showed marked generalized edema and ascites (Fig. 16), tiny orange

FIG. 14. Case 11, at 17 mo. of age. Idiopathic familial hyperlipemia with secondary xanthomas (Buerger-Grutz syndrome). FIG. 15. Case 11. Close-up of orange papules on left leg. Other groups of xanthomas were found across shoulders and chest. At this time patient's blood contained 3% fat.

papules over the lower abdominal wall and thighs, and definite orange nodules on the elbows (Fig. 17). Biopsy of one of these elbow xanthomata demonstrated collections of pale-staining sudanophilic monocytes. Laboratory examination showed a turbid serum with 5.7% fat and a cholesterol of 1156 mg./100 cc. NPN was 28.4 mg./100 cc., serum protein xanthomata were transient, having largely disappeared in 7 days, at which time the total serum cholesterol was still 1122 mg./100 cc. (see table 4). Two weeks later they were gone completely and they did not reappear. Four months later, during a severe relapse, he developed intestinal obstruction and died. Postmortem examination revealed marked kidney damage, but no special evidence of lipid deposition in the blood vessels or elsewhere.

Case 13. C. H., another boy similar to Case 12. In this child, edema appeared 2 wk. after a respiratory infection at the age of 3 4/12 yr. The skin was clear until 10 mo. later, when many tiny orange papules were noted, especially on the knees and lower legs. Two months later, at a time when his nephrotic syndrome was still in moderate relapse, distinct orange nodules were present on the knees and the serum cholesterol was markedly elevated (table 4). His NPN at that time was 41.5 mg./100 cc., and the urine had a 3+ albumin and many red blood cells, white blood cells and casts.

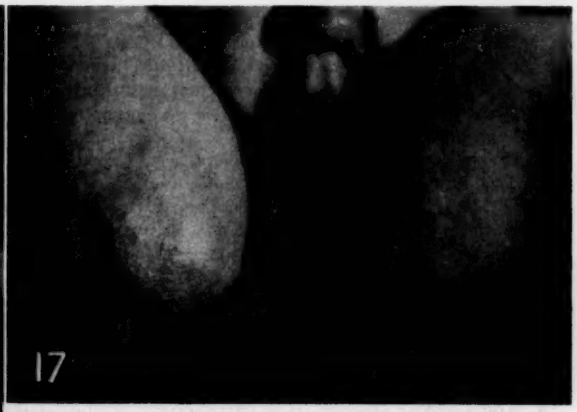

FIG. 16. Case 12, at 3 1/12 yr. of age. Nephrotic syndrome with secondary xanthomas. Generalized edema had been slowly accumulating for 4 mo. FIG. 17. Case 12. Close-up of small orange nodules on elbows. One of these lesions was biopsied and showed large numbers of pale-staining sudanophilic monocytes.

4. Hypothyroidism: Moderate increases of cholesterol and other serum lipids are considered characteristic of clinical hypothyroidism. Cholesterol has long been thought to be one of the best indices of thyroid function, although Peters[65] would question this status. No reports were found in the pediatric literature of secondary xanthomas in cretinism or juvenile myxedema, but there are two reports available for adults of xanthoma-tuberosum-like lesions which appeared at an interval after symptoms of myxedema began, and allegedly improved on thyroid therapy.[66, 67]

5. Chronic Obstructive Liver Disease: A modification of the serum lipid values is not unusual in chronic obstructive liver disease. Commonly the total cholesterol level is elevated, with a subsequent fall in the per cent of cholesterol esterified if parenchymal liver damage is marked; elevation of serum phospholipids is also frequent.[68] Eusterman and Montgomery[69] have described eruptive xanthomata forming in patients with post-

operative bile duct stricture. Rarely pediatrics patients with "partial biliary atresia" survive and develop skin xanthomas. A patient is presented here with xanthomas and biliary obstruction which appeared to be on a diffuse, intrahepatic, presumably congenital but possibly inflammatory basis.

Case 14. T. D., male. This patient had slight jaundice observed in the neonatal period, gradually increasing until 3 mo. of age, when it had become severe and persistent. At 7 mo. of age, he was laparotomized at another hospital where "atresia of the bile ducts" was observed and no surgical repair attempted. Following this he remained deeply jaundiced but in fair general health. At 2 5/12 yr. he was re-explored at the Children's Medical Center. The liver was described as about normal size and biopsy showed "biliary stasis" and extensive replacement by fibrous tissue. The gall bladder was small and the extrahepatic biliary system was atrophied but demonstrated to be patent. A diagnosis of intrahepatic biliary obstruction was made and no surgical therapy attempted. The total serum bilirubin was 25.1 mg./100 cc. at that time, and the prothrombin time 18″ versus a normal control of 12″. His general condition again continued fair, with very slow weight gain. At about 3 yr. of age, whitish "pimples" appeared on each elbow which became yellow and increased in number. At 3 5/12 yr., yellow plaques appeared on the skin of each palm, which have varied in visibility since. Past history otherwise negative. Family history negative for liver or xanthomatous disease, but diabetes mellitus present. Physical examination at 3 7/12 yr. showed an alert, slightly irritable boy weighing 11.3 kg., with deeply icteric skin and sclerae. The liver and spleen were each firm and enlarged. Each elbow had about a dozen orange nodules and small orange-pink xanthomas could be found in many areas on the trunk and neck. Both palms had small yellowish plaques in the subcutaneous tissue. Laboratory examination showed a total serum bilirubin of 20.6 mg./100 cc.; see table 4 for the serum lipid values.

6. Von Gierke's Disease: It is characteristic of von Gierke's disease patients ("hepatic form of glycogen storage disease") to have an elevation of serum lipids, and occasionally the lipemia is quite marked.[12] As in diabetes mellitus, the hyperlipemia is presumably a function of the reduced usable carbohydrate available for combustion. The formation of eruptive xanthomas in von Gierke's disease has been reported in one instance;[70] another is given below.

Case 15. R. L. D., female infant. Patient's liver was noted to be enlarged soon after birth, and a gradually increasing degree of hepatomegaly with marked abdominal protuberance has been a constant observation. Orange "pimples" were noted on the elbows at 7 mo. of age. She had a ravenous appetite but only fair weight gain. Her development was adequate until about 5 mo. but has regressed somewhat since then. She was first seen here at 8 mo. because of a skull fracture following a head injury. She is the only pregnancy of these parents, who are not related. The father's family history is negative, but the mother's parents were first cousins. The maternal grandmother had 2 brothers with poor progress and markedly enlarged abdomens in infancy; one died at the age of 3 yr., the other improved and is now a successful businessman in Africa. The mother's serum cholesterol on 3 occasions was 277, 395 and 440 mg./100 cc.

Physical examination at 8 mo. showed an irritable but fairly well nourished infant weighing 7.0 kg. (Fig. 18). There were bilateral depressed parietal skull fractures. The abdomen was markedly protuberant, with prominent veins, and a liver which extended to the pelvic brim. The spleen was moderately enlarged. There were a dozen or so orange nodules on each elbow (Fig. 19) and one on the left thigh. There was diffuse adenopathy. Neurologic examination was normal, including the fundi. Oral glucose tolerance test showed a fasting level of 60 mg./100 cc. with a rise to 235 in 30 min., 200 in 60 min. and 120 in 3 hr. Response to epinephrine showed a fall and no rise in blood sugar. On examination during fasting the blood sugar gradually fell to 25 mg./100 cc. in 7 hr. with acidotic breathing noted and a marked ketonuria. Blood glycogen level was 9.4 mg./100 cc. (Dr. Richard Wagner, Boston Floating Hospital). Blood lipids were elevated, with a creamy serum (see table 4). RGs showed hepatomegaly, normal kidney function with diffusely enlarged kidneys, normal heart size and undermineralization of the bones with widening of the bone ends. At laparotomy the liver was pale yellow-pink and the liver biopsy showed increased fat and glycogen with normal liver architecture.

At 15 mo. of age the child had improved on a near normal diet (some restriction of fat). The abdomen was smaller, the xanthomata nearly gone, and her development much improved.

7. Other Conditions: No reports were found of xanthomas in the lipemia which accompanies marked chronic anemia.[71] There is also an occasional example of lipemia in Niemann-Pick's disease,[12] but no xanthomas have been observed in this condition or in Gaucher's disease.[72]

FIG. 18. Case 15, 9 mo. of age. Von Gierke's disease with eruptive xanthomas. FIG. 19. Case 15. Close-up of orange papules on elbows, first noted at 7 mo. of age. Serum lipid level at this time was 2.2 gm./100 cc.

DIAGNOSIS

Secondary xanthomas may resemble mild instances of either xanthoma disseminatum or tuberosum, as described above. Typically these lesions are small orange papules, occasionally with a narrow hyperemic border. There is some predilection for extensor surfaces of the extremities. Their most prominent characteristic is rapid appearance and disappear-

ance with the changing clinical status of the patient. In these conditions analysis of serum lipids will result in better documentation of the case and better evaluation of therapy.

Prognosis and Treatment

There is no treatment for the secondary xanthomas per se, but they may serve as an index of the activity of the underlying disease. In idiopathic familial hyperlipemia and obstructive liver disease, restriction of dietary fat may be advisable. The prognosis depends on the primary disease.

Discussion

Two general groups of patients with xanthomas are found: those with normal serum lipids and those with hypercholesterolemia and hyperlipemia. Although much biochemical data has been accumulated, adequate etiologic conclusions cannot yet be drawn. While each of the clinical groups is distinct when typical patients are considered, occasional patients are found with xanthomas that are difficult to classify. There is also a remarkable overlapping in the histologic appearance of these various lesions. No special type of lipid-storing "foam cell" is limited exclusively to any of the four clinical groupings (and not even between those with normal as opposed to high serum lipids). We lack specific information as to why cholesterol (and other lipids) are accumulated in these cells. Polano[44] uses the term "cholesterophilia" to describe the alleged attraction of the cells for lipid. Sobotka[73] would have us believe that an interruption of the normal cyclical transformation among related lipid substances ("trans-esterification") would allow accumulation of one lipid at the expense of others. At any rate, the conception of the xanthoma cell or foam cell as a common participant in pathologic reactions seems justified, probably in a more complicated role than the mere scavenging of excess or abnormal lipid.

Summary

It is suggested that the term "xanthoma" be limited to lesions containing a high percentage of lipid as cholesterol and, since these are small yellow tumors, this seems appropriate.

The patient with these lesions deserves careful clinical study, and an estimation of serum lipids. If possible, total serum lipid determination with partition is desirable, especially in the obscure cases. At least an accurate estimation of serum cholesterol is needed before a logical prognosis and course of treatment can be provided. The Schoenheimer-Sperry cholesterol method has the widest acceptance.

Patients with xanthomas can be divided into those with normal serum lipids and those with elevated lipids.

A. Xanthoma disseminatum lesions are the most frequent and the most benign, and are associated with normal serum cholesterol values.

B. Xanthomas without elevation of serum lipids are also found in patients with the "eosinophilic granuloma syndromes," and occasionally with other chronic diseases.

C. In xanthoma tuberosum the serum cholesterol is markedly elevated, and the frequent cardiac involvement gives the full-blown patient a poor prognosis.

D. Secondary or eruptive xanthomas can accompany most of the conditions with chronic hyperlipemia irrespective of the cause, but they are most common in diabetes mellitus and idiopathic familial hyperlipemia.

Another case of idiopathic familial hyperlipemia in an infant is reported, with a total serum lipid level of 6.2%, as well as two cases of the nephrotic syndrome in childhood with secondary xanthomas, a case of xanthomas complicating chronic obstructive liver disease, an example of eruptive xanthomata in von Gierke's disease, and a description of a diabetic girl with a serum total lipid level of 19.4%.

The basic cause for the accumulation of cholesterol in any of these conditions is unknown. Surgical removal of the lesions is rarely advisable, and dietary treatment is indicated only in certain of the hypercholesterolemic syndromes.

ACKNOWLEDGMENT

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REFERENCES

1. Thannhouser, S. J., and Magendantz, H., Different clinical groups of xanthomatous diseases: Clinical physiological study of 22 cases, Ann. Int. Med. **11**:1662, 1938.
2. Montgomery, H., and Osterberg, A. E., Xanthomatosis: Correlation of clinical, histopathologic, and chemical studies of cutaneous xanthomas, Arch. Dermat. & Syph. **37**:373, 1938.
3. Urbach, E., and Hill, W. R., Proposed classification of cutaneous lipidoses, Arch. Dermat. & Syph. **42**:68, 1940.
4. Smith, W. F., On xanthomas, or vitiligoidea, J. Cutaneous Med. **3**:241, 1869.
5. Cowdry, E. V., Laboratory Technique in Biology and Medicine, Baltimore, Williams & Wilkins Company, 1948, p. 221.
6. Schoenheimer, R., and Sperry, W. M., Micromethod for determination of free and combined cholesterol, J. Biol. Chem. **106**:745, 1934.
7. Sperry, W. M., Schoenheimer-Sperry method for determination of cholesterol, privately distributed communication, April 1945.
8. Boyd, E. M., Oxidative micro-estimation of blood lipids, Am. J. Clin. Path. (Tech. Supp.) **8**:77, 1938.
9. May, C. D., Blackfan, K. D., McCreary, J. F., and Allen, F. H., Clinical studies of vitamin A in infants and in children, Am. J. Dis. Child. **59**:1167, 1940.
10. Hodges, R. F., Sperry, W. M., and Andersen, Dorothy H., Serum cholesterol values for infants and children, Am. J. Dis. Child. **65**:858, 1943.
11. Thomas, E. M., Total and fractional blood lipid levels in diseases of childhood, Am. J. Dis. Child. **74**:563, 1947.
12. Thannhauser, S. J., Lipidoses: Diseases of Cellular Lipid Metabolism, New York, Oxford University Press, 1950.
13. Lamb, J. H., and Lain, E. S., Nevo-xantho-endothelioma: Its relationship to juvenile xanthoma, South. M. J. **30**:585, 1937.
14. Senear, F. E., and Caro, M. R., Nevoxanthoendothelioma or juvenile xanthoma, Arch. Dermat. & Syph. **34**:195, 1936.
15. McDonagh, J. E. R., Contribution to our knowledge of naevo-xanthoendotheliomata, Brit. J. Dermat. **24**:85, 1912.
16. Blank, H., Eglick, P. G., and Beerman, H., Nevoxanthoendothelioma with ocular involvement, PEDIATRICS **4**:349, 1949.
17. Charache, H., Congenital xanthoma tuberosum, Am. J. Cancer **31**:563, 1937.
18. Soehring, K., Xanthelasmatosis in early childhood, Monatschr. f. Kinderh. **77**:315, 1939.
19. Bloch, B., Metabolism, endocrine glands, and skin diseases, with special reference to acne vulgaris and xanthoma, Brit. J. Dermat. **43**:61, 1931.
20. Michael, J. C., and Nicholas, H. O., Blood lipids in xanthoma, Arch. Dermat. & Syph. **29**:228, 1934.

21. Gofman, J. W., and others, Role of lipids and lipoproteins in atherosclerosis, Science **111**:166, 1950.
22. Gruenfeld, G., and Seelig, M. G., Nature of so-called xanthoma: Critical review, Arch. Path. **17**:546, 1934.
23. Plewes, L. W., Nature and origin of xanthoma cell, Arch. Path. **17**:177, 1934.
24. Stewart, M. J., On cellular reactions induced by local deposits of cholesterin in tissues, J. Path. & Bact. **19**:305, 1914-15.
25. Biebl, M., Xanthomatous inflammation in surgical diseases and in "metabolic blastomas," Arch. f. klin. Chir. **190**:33, 1937.
26. Osterlind, S., Xanthomatous pyelonephritis, Acta chir. Scandinav. **90**:368, 1944.
27. Gross, R. E., and Wolbach, S. B., Sclerosing hemangiomas: Relationship to dermatofibroma, histiocytoma, xanthoma and to certain pigmented lesions of skin, Am. J. Path. **19**:533, 1943.
28. Foot, N. C., Possible relationship between primary cutaneous xanthomas and melanomas, Am. J. Cancer **37**:425, 1939.
29. Farber, S., Nature of some diseases ascribed to disorders of lipid metabolism, Am. J. Dis. Child. **68**:350, 1944.
30. Cowie, D. M., and Magee, M. C., Lipoids and lipoid disease. III. Lipoid content of tissues in Schüller-Christian disease (xanthomatosis) and review of literature on lipoid content of human tissues, Arch. Int. Med. **53**:391, 1934.
31. Discherl, W., Cholesterol and its esters in xanthomas and their isolation, Ztschr. f. physiol. Chem. **264**:34, 1940.
32. Rowland, R. S., Christian's syndrome and lipoid-cell hyperplasias of reticulo-endothelial system, Ann. Int. Med. **2**:1277, 1929.
33. Thannhauser, S. J., Serum lipids and their value in diagnosis, New England J. Med. **237**:515 and 546, 1947.
34. Biedermann, W., and Höfer, K., Ergebnisse der Zochtung von menschlichen Xanthomgewebe in vitro, Arch. f. exper. Zellforch. **10**:93, 1930.
35. Pinkus, H., Copps, L. A., Custer, S., and Epstein, S., Reticulogranuloma, Am. J. Dis. Child. **77**:503, 1949.
36. Cook, C. D., Smith, H. L., Giesen, C. W., and Berdez, G. L., Xanthoma tuberosum, aortic stenosis, coronary sclerosis and angina pectoris, Am. J. Dis. Child. **73**:326, 1947.
37. Rigdon, R. H., and Willeford, G., Sudden death during childhood with xanthoma tuberosum, J. A. M. A. **142**:1268, 1950.
38. Svendsen, M., Are supernormal cholesterol values in serum caused by dominantly inherited factor? Acta med. Scandinav. **104**:235, 1940.
39. Fliegelman, M. T., Wilkinson, C. F., and Hand, E. A., Genetics of xanthoma tuberosum multiplex, Arch. Dermat. & Syph. **58**:409, 1949.
40. Aldersberg, D., Parets, A. D., and Boas, E. P., Genetics of atherosclerosis, J. A. M. A. **141**: 246, 1949.
41. Thannhauser, S. J., Xanthomatoses, J. Mt. Sinai Hosp. **17**:79, 1950.
42. Pollitzer, S., and Wile, U. J., Xanthoma tuberosum multiplex, J. Cutaneous Dis. **30**:235, 1912.
43. Levin, E. A., and Sullivan, M., Familial xanthoma: Report on 3 of 5 siblings with xanthoma tuberosum multiplex, Arch. Dermat. & Syph. **33**:967, 1936.
44. Polano, M. K., Pathogenesis of cutaneous cholesteroses, Arch. f. Dermat. u. Syph. **174**:213, 1936.
45. Chaikoff, I. L., McGavack, T. H., and Kaplan, A., Blood lipids in postabsorptive state and after ingestion of fat in disseminated cutaneous xanthomata, J. Clin. Investigation **13**:1, 1934.
46. Hutchinson, J., Sangster, A., and Crocker, H. R., Report on cases of xanthoma, Proc. Path. Soc. London **33**:376, 1882.
47. Sperry, W. M., and Schick, B., Essential xanthomatosis: Treatment with cholesterol-free diet in two cases, Am. J. Dis. Child. **51**:1372, 1936.
48. Okey, R., Cholesterol content of foods, J. Am. Dietet. A. **21**:341, 1945.
49. Versar, F., and McDougall, E. J., Absorption from Intestine, London, Longmans, Green & Co., 1936, chap. 10.
50. Curtis, A. C., and Berger, J. P., Effect of feeding lipotropic substance to patients with xanthelasma, Arch. Dermat. & Syph. **52**:252, 1945.

51. Schmidt, H. G., Problem of essential xanthomatosis: Disorders of cholesterol metabolism, Ztschr. f. klin. Med. **136**:738, 1939.
52. Delevett, A. F., and Bruger, M., Plasma lipids in primary and secondary hypercholesteremia: Effect of lipotropic substances, Arch. Int. Med. **81**:859, 1948.
53. Marble, A., and Smith, R. M., Blood lipids in lipaemia retinalis, Arch. Ophth. **15**:86, 1936.
54. McCoord, A. B., and Clausen, S. W., Personal communication to the author.
55. Lefkovits, A. M., and Young, J. M., Lipemia retinalis and xanthoma diabeticorum in diabetes mellitus, Ann. Int. Med. **32**:755, 1950.
56. Joslin, E. P., and others, Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1946, p. 594.
57. Major, R. H., Xanthoma diabeticorum, Bull. Johns Hopkins Hosp. **35**:27, 1924.
58. Chapman, F. D., and Kinner, T. D., Hyperlipemia: "Idiopathic lipemia," Am. J. Dis. Child. **62**:1014, 1941.
59. Holt, L. E., Aylward, F. X., and Timbus, H. G., Familial lipemia of undetermined origin, J. Clin. Investigation **15**:451, 1936.
60. Kennedy, R. L. J., and Collett, R. W., Chronic relapsing pancreatitis and hyperlipemia, Am. J. Dis. Child. **78**:80, 1949.
61. Bernstein, S. S., and others, Metabolic observations on child with essential hyperlipemia, J. Pediat. **14**:570, 1939.
62. Thannhauser, S. J., and Stanley, M. M., Serum fat curves following oral administration of I^{131}-labeled neutral fat to normal subjects and those with idiopathic hyperlipemia, Tr. A. Am. Phys. **62**:245, 1949.
63. Hopgood, W. C., Idiopathic hyperlipemia, New England J. Med. **238**:429, 1948.
64. Friedman, R., Nelson, W. E., Stritzler, C., and Roxby, J. B., Xanthoma eruptivum secondary to lipid nephrosis, Arch. Dermat. & Syph. **60**:828, 1949.
65. Man, E. B., and Peters, J. P., Significance of serum cholesterol in thyroid disease, J. Clin. Investigation **29**:1, 1950.
66. Craig, L. S., Lisser, H., and Soley, M. H., Myxedema with extreme hypercholesterolemia: Case complicated by xanthoma tuberosum, J. Clin. Endocrinol. **4**:12, 1944.
67. Sweitzer, S. E., and Winer, L. H., Xanthoma tuberosum and myxedema, Arch. Dermat. & Syph. **42**:419, 1940.
68. Ahrens, E. H., and Kunkel, H. G., Relationship between serum lipids and skin xanthomata in 18 patients with primary biliary cirrhosis, J. Clin. Investigation **28**:1565, 1949.
69. Eusterman, G. B., and Montgomery, H., Disorders of liver and extrahepatic biliary ducts associated with cutaneous xanthomas and hyperlipemia, Gastroenterology **3**:275, 1944.
70. Beumer, H., Cholesterinstoffwechsel bei Glykogenose, München. med. Wchnschr. **84**:1007, 1937.
71. Boggs, T. R., and Morris, R. S., Experimental lipemia in rabbits, J. Exper. Med. **11**:553, 1909.
72. Montgomery, H., Cutaneous manifestations of diseases of lipoid metabolism, M. Clin. North America **24**:1249, 1940.
73. Sobotka, H., Chemical differentiation of Tay-Sachs disease and other lipidoses, J. Mt. Sinai Hosp. **9**:795, 1944.

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SPECIAL ARTICLE

AMERICAN BOARD OF PEDIATRICS

IT IS desirable that as many people as possible should know how much care and thought is given both to the preparation and to the subsequent analysis of the examinations of the American Board of Pediatrics. For this reason the following comments on the examination of January 1950 are published for general information.

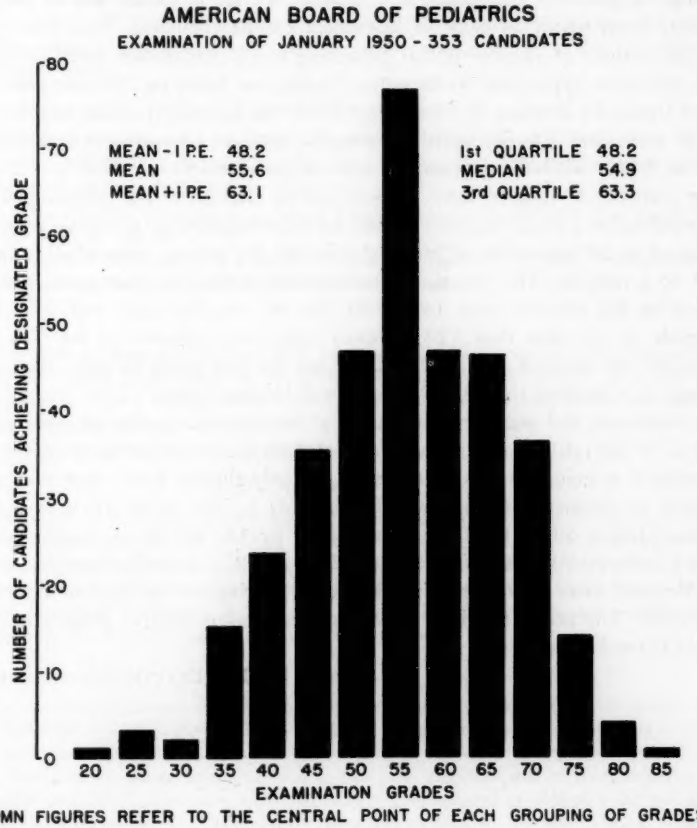
The written examination of the American Board of Pediatrics given in January 1950 has been subjected to statistical analysis. It is proposed that all subsequent examinations be analyzed in a similar or improved way in order to learn whether modifications are accomplishing the purpose for which they were made and in the endeavor to improve the accuracy of the grading. Some of the results of this first statistical analysis may be of interest and may help in understanding how reliable the examination in its present form is.

The examination consisted of 200 false and true statements and was taken by 353 candidates. A majority of the candidates marked all of the statements as being either false or true. That is to say, they marked with confidence when they knew and guessed when they did not know. However, a fairly large number of candidates refused to commit themselves at all when they did not know. It is of interest that one of the highest grades ever earned in these examinations was achieved by a candidate also distinguished by having refused to commit himself on the largest number of statements. The method of grading is one which yields essentially the same figure whether or not the candidate elects to guess. To the number of correctly answered statements one adds half the number of unanswered statements and from the total subtracts 100; the remainder is the grade.

The distribution of the grades earned by the 353 candidates is shown on the accompanying chart (histiogram). The form of the histiogram suggests that we may be dealing with an essentially normal distribution. The suggestion is corroborated by additional data on the chart. Medians and quartiles have been determined; these statistics are quite independent of an assumption of normality of distribution. The median is a grade which divides the candidates in half in such a way that 50% have lower grades and 50% have higher grades. The median is given as 54.9. Since no candidate can earn a grade ending in the decimal 9. the meaning of the decimal deserves a word of explanation. Let us suppose that 10 candidates earned a mark of exactly 54 and that 9 must be placed in the lower one-half and 1 in the upper one-half to effect the equal division of the total number of candidates about a median. Statistically this is done by using the decimal 9. Quartiles are determined in a similar way. Since one-fourth of the grades are below the first quartile and one-fourth are higher than the third quartile, it follows that half the grades are between the first and third quartiles. Again let us stress the point that these statistics are determined by actual counting of the grades and do not depend on the type of distribution, normal or otherwise.

In contrast, the fidelity with which a mean (or average) and its standard deviation describe a distribution does depend upon normality. These statistics have also been computed for the 353 grades. However, instead of the standard deviation, a statistic derived

from it, the probable error of the distribution, has been used in preparing the chart. This has been done because the range covered by the mean plus and minus one probable error will for normally distributed data encompass 50% of the figures. Direct comparison with the quartile figures is then possible. The essential identity of the ranges obtained by the two methods of computation speaks for the normality of the distribution of these 353 grades.



There are of course more elaborate and more exact methods of testing for normality of distribution. In the present case the good to be gained does not justify the labor.

So much for the manner in which these 353 candidates are distributed with respect to grades. A lowest mark of 17.5 and a highest mark of 85 provide ample range for differential selection of candidates. There remains the important question of how accurately the examination defines the position of the individual candidate against the background of all of the candidates. To obtain information on this point all of the papers were re-examined in such a way that each candidate could be assigned two grades. One grade was based on the odd-numbered statements; the other grade was determined from the even-numbered statements. The resulting 706 grades were then studied by the method of

analysis of variance. The method is one in which total variability (total variance) is expressed as the sum of the squares of the differences between each grade and the mean for all of the grades. The total variance can then be divided into the three components contributing to it. These components are: variability of ability among the 353 candidates; an actual difference in difficulty between the odd-numbered and even-numbered statements; a residual variability which measures the degree of success of the examination in fixing the grades of the individual candidate. We are interested here in this residual variability from which an error of assessment can be computed. The error calculated from the analysis of variance is that pertaining to an examination based on 100 statements. The error appropriate to the entire examination based on 200 statements is easily derived from it by dividing by the square root of two. Calculated in this way the standard error of assessment (usually called the standard error of measurement or S.E.M.) turns out to be 5.028. Similarly, the probable error of measurement or P.E.M. is 3.391.

The practical meaning of these statistics can be clarified in the following way: If it were possible for a single candidate to take an unlimited number of similar examinations, each based on 200 statements of identical difficulty, the average value of all of the grades would be a constant. This constant is conveniently termed the true grade. For a single examination the odds are even, i.e., 50-50, that the assigned grade will differ from the true grade by not more than 5.03. Derived from these statistics are the facts that one time in 20 the assigned grade will differ from the true grade by more than 9.85 and that once in a hundred times the difference will be greater than 12.95.

An additional and possibly useful item of information can be gleaned from these statistics. If the relative abilities of two candidates are to be compared on the basis of their written examination grades, the odds are only slightly better than even of a real difference of abilities if the grades differ by only 5. We can be fairly sure of a real difference (odds, 20 to 1) if the grades differ by 14; we can be highly sure (odds, 100 to 1) of a real difference if the grades differ by 18. It is hardly necessary to add that the differences refer only to relative abilities in scoring on this type of false and true examination. The extent to which the differences measure relative abilities in pediatrics remains as the $64 question.

THE EXAMINATIONS COMMITTEE

NEWS AND ANNOUNCEMENTS

AAAS Philadelphia Meeting, Dec. 26 to 31, 1951

The 118th Meeting of the American Association for the Advancement of Science, the Annual Meeting for 1951, will include programs for all 18 of the Association's sections and about 45 participating societies. Programs of particular interest to those in pediatrics, medicine and experimental biology include:

Sectional Programs

Section C—Chemistry: 11 sessions, including one on Medicinal Chemistry—Dec. 28.

Subsection Nm—Medicine: 4-session symposium on Abnormalities of Lipid Metabolism, with special reference to arteriosclerosis—Dec. 29 and 30

Subsection Nd—Dentistry: 3 sessions, including a symposium on Fluoridation as a Public Health Measure, Dec. 28 and 29

Section N—Society for Research in Child Development: 4 sessions including a symposium, Biochemistry of Nutrition in Human Growth—Dec. 27.

* * *

The American Academy for Cerebral Palsy announces that its Annual Meeting will be held in Boston, at the Copley Plaza Hotel, on Friday and Saturday, Nov. 16 and 17, 1951. The Friday afternoon scientific session will be an open meeting and all physicians interested in the problem of cerebral palsy are cordially invited to attend. The program will include the presidential address, "The Cerebral Palsy Problem in 1951," by Bronson Crothers.

* * *

The University of Toronto has awarded the Charles Mickel Fellowship for the year 1951 to Dr. Norman Gregg, the Institute of Child Health of the University of Sydney, Australia, for his incrimination of maternal rubella as a cause of congenital defects. This Fellowship is awarded to "that member of the medical profession who is considered by the Council of the Faculty of Medicine of the University of Toronto to have done most during the preceding ten years to advance sound knowledge of a practical kind in the medical art or science."

* * *

The University of Pittsburgh has announced the appointment of Dr. Samuel M. Wishik as Professor of Maternal and Child Health. Dr. Wishik and his staff will develop a program of teaching and research in maternal and child health. They will be available for co-operation with official and voluntary organizations and agencies interested in this field. Emphasis will be given to public health administration and close co-operation will exist with the departments of obstetrics and pediatrics in the School of Medicine at the University for their contribution to the more clinical features of health programs for mothers and children. Dr. Wishik's most recent position has been that of Director of Child Health in the City of New York.

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The Leonard Parsons Memorial Lectureship Appeal

"No one contributed more to the remarkable development of Paediatrics and the Birmingham Medical School than the late Sir Leonard Parsons. Thirty years ago he was one of the few who understood that the time had come for clinical practice to examine its traditional empiricism in the light of modern progress in science and the humanities, and he was inspired by the ideal of a medical school and a great hospital as an integral part of a University. For many years he gave himself unsparingly to the unremitting work that is the necessary prelude to great adventure. The achievements of recent years have justified his faith and labour.

"The career of Leonard Parsons, however, is particularly remarkable because during this period of constant pre-occupation with administrative business, he not only did his full share of duty at his hospitals and in practice, but in addition undertook fundamental research and made significant advances in the knowledge of the diseases of children. These brought him fame and, ultimately, the Fellowship of the Royal Society. He was so modest that formal recognition of his achievement always surprised him as much as it gave him pleasure. He never preached, but the example of his simple and unswerving Christian faith made him an abiding influence for good, particularly when he was Dean. What he did in Birmingham is comparable with Lister's work in Glasgow.

"Tradition is the essence of great institutions and tradition is based on the work of men. Leonard Parsons now belongs to the ages, but the University wishes to keep his memory fresh as a stimulus to the young who will build on the foundations he so securely laid. To that end it is proposed to found a lectureship and we desire to collect sufficient money so that year by year men of distinction from all over the world may be enabled to come to Birmingham to speak in his school on subjects related to the problem so near his heart—the health of the child."

A gift form may be obtained which will enable the University to recover Income Tax on the subscription or the gift may be sent directly to: University of Birmingham, Ladywood Road, Edgbaston, Birmingham (16), England.